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Chemical and Physical Structure of Polymers as Carriers for Controlled Release of Bioactive Agents: A Review

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I. INTRODUCTION

In a controlled release system a drug, pesticide, or other bioactive agent is incorporated into a carrier, generally a polymeric material. The rate of release of the substance is determined by the properties of the polymer itself and is only weakly dependent on environmental factors (such as the pH of bodily fluids). Controlled release systems are capable of delivering substances slowly and continuously for up to several years.

These controlled release systems represent a relatively new development that evolved out of a continuing need to prolong and better control drug administration. The significance of such systems can be appreciated by considering typical drug levels resulting from conventional drug formulations (tablets, sprays, injections). In most cases, drug levels reach a maximum and then fall to a minimum, at which point repeated administration becomes necessary. However, if the maximum and minimum drug concentrations fall above or below the toxic level or minimum effective level, respectively, alternating periods of toxicity or inefficacy can result (Fig. 1A). This is particularly problematic if the toxic and minimum effective levels are close together. The goal of a controlled release system is to maintain the drug concentration between these two levels from a single dosage form. A controlled release system should release drug continuously in a fixed, predetermined pattern for a desired time period (Fig. 1B). Ideally, this should result in a uniform drug concentration as a function of time, require smaller dosages, and cause fewer side effects.

In order for the drug to be taken up by the desired site of the body, several events must occur. The drug must first be released from the device, it must then diffuse from the surface of the device to the surrounding bloodstream, and eventually it must

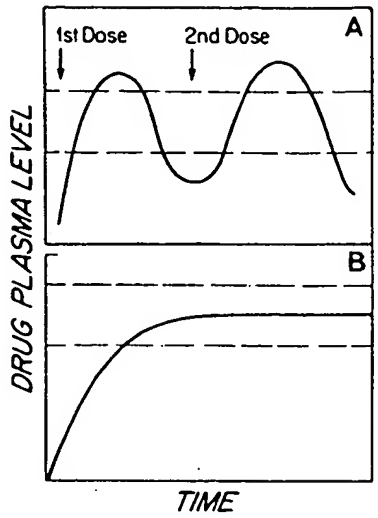

FIG. 1. Plasma drug levels from a standard dosage form (A) and a controlled release dosage form (B). The dashed lines represent the range between the toxic drug level and the minimum effective drug level.

be transported to its target. Ideally, the first of these steps should be rate-limiting so that release is totally dependent on the device itself and not on the surrounding environment.

Early efforts to prolong release involved the use of slowly dissolving coatings, complexes of drugs with salts or ion-exchange resins, suspensions, emulsions, or compressed tablets. These systems were considered sustained release formulations and served to prolong the length of time before the drug concentration in bodily fluids fell below the minimum effective level. However, such methods did not generally permit long-term release (greater than one day) and were subject to wide variations in release rates as a function of environmental conditions. Controlled release formulations were first used in the agricultural industries for low molecular weight fertilizers, pesticides and antifoulants in the 1950s [1]. In the 1960s these approaches were extended into the medical field [2, 3]. By the mid-1970s, controlled release formulations for large molecular weight drugs (e.g., polypeptides) were designed [4]. Developments in this field have been numerous in the past decade. In this article we review the chemical and physical characteristics of controlled release systems. There are four general mechanisms which may be used for convenient classification of controlled release systems.

1. Diffusion controlled
   a) Reservoirs (membranes)
   b) Matrices (monoliths)
2. Chemically controlled
   a) Erosion
   b) Pendant chain
3. Solvent activated
   a) Osmotic pressure
   b) Swelling
4. Magnetically controlled

Each of these mechanisms is discussed below; a review of the applications of these systems follows. Since diffusion is the predominant mechanism utilized in controlled release systems and because diffusion takes place in all controlled release systems, an introductory section on diffusion through polymers is provided.

It should be noted that there is no singularly ideal release profile for all drugs. In many cases, constant release is desirable. In other cases, a high initial dose followed by a declining dose may produce the most desired therapeutic effect. Finally, it may be preferable for certain drugs (e.g., hormones) to exhibit a modulated drug release profile. Similarly, there is no singularly ideal release mechanism for all drugs. In some cases it is desirable to have the systems bioerode so there will be no residue left. In other cases, however, the uncertainty that all drug and polymer will be completely gone at the necessary time implicates the use of a nonerodible diffusion controlled system. Other systems may also be desirable depending on the treatment under consideration.

II. DIFFUSION OF BIOACTIVE AGENTS THROUGH POLYMERS

The release behavior of bioactive agents is the result of diffusional phenomena in the polymer and mass transfer limitations at the polymer/liquid interface. Therefore, modification or design of controlled release systems requires understanding of mechanisms of solute diffusion through polymeric materials [5–7].

Regardless of the type of controlled release system the diffusion coefficient of the bioactive agent through the polymer depends on structural and morphological parameters. Theoretical analyses have reviewed the effect of polymer structure on solute diffusivity [8–14]. Solute diffusivity may be also dependent on the concentration of the solute in the polymer [15, 16].

A. Macroscopic Analysis

Solute diffusion through and release from polymeric systems can be analyzed in terms of the Fickian diffusion theory [15], which for one-dimensional diffusion may be written according to

$$J_i^* = -D_{ip}\, dc_i/dz \tag{1}$$

$$\partial c_i/\partial t = D_{ip}\, \partial^2 c_i/\partial z^2 \tag{2}$$

where J_i^* is the molar flux of bioactive agent with respect to the molar average velocity of the system, c_i is its concentration, t is time, z is position through a film, and D_{ip} is the concentration-independent solute diffusion coefficient through the polymer.

Equations (1) and (2) are often used to predict release behavior in the absence of mass-transfer limitations [7, 11]. Equation (1) is used for description of reservoir-type, diffusion controlled systems at steady-state diffusion and release. Equation (2) is employed when describing release from slabs, spheres, cylinders, and other geometries for matrix-type, diffusion controlled systems (see Section III).

For concentration-dependent diffusion coefficients of the solute through the polymer, Eq. (2) may be rewritten and solved with appropriate boundary conditions (see Section III):

$$\partial c_i/\partial t = \partial/\partial z \{D_{ip}(c_i)\, \partial c_i/\partial z\} \tag{3}$$

The concentration dependence of D_{ip} is affected by the structural characteristics of the polymer. A useful function is an exponential dependence of D_{ip} on solute concentration [16] which is expressed by Eq. (4), where $D_{s'}$ and $c_{s'}$ are the surface diffusion coefficient and concentration, respectively, and β is a constant:

$$D_{ip}(c_i) = D_{s'} \exp\{\beta(c_i - c_{s'})\} \tag{4}$$

Other expressions of D_{ip} based on free-volume theories can be found in Crank [15].

B. Classification of Polymer Membranes

Transport through polymer membranes has been reviewed [8, 17–20]. Polymeric films and membranes can be classified into three general categories with respect to solute diffusion [21].

i. Macroporous membranes. These are membranes with large pores, usually in the range of 0.1 to 1.0 μm. Membranes with pores as small as 500 Å may be included in this category. Although diffusion does occur through these membranes, convection may be the predominant mass transfer mechanism.

ii. Microporous membranes. These are membranes with pore size in the range of 100 to 500 Å. The pores are slightly larger than macromolecular bioactive agents. Under these conditions the diffusional path of the solute through the pores is restricted by the geometrical characteristics of the porous structure and by solute partitioning in the pore walls.

iii. Nonporous (gel) membranes. The "pores" of these membranes are of molecular level and they are formed by the macromolecular chains of the entangled, cross-linked, or crystalline chain network of the polymer. Molecular diffusion is the only mode of mass transport, since convection is negligible. The space between macromolecular chains has been called the mesh size.

C. Macroporous Polymer Systems

Diffusion in macroporous polymer systems may be described by Eq. (1) where an effective diffusion coefficient is substituted for D_{ip}. Integration of this equation between the two phases external to the membrane gives

$$J_i^* = D_{eff}\,\Delta c_i/\delta \tag{5}$$

where D_{eff} is defined by

$$D_{eff} = D_{iw}\,\varepsilon/\tau \tag{6}$$

Here D_{iw} is the diffusion coefficient of the bioactive agent in water, ε is the porosity (void fraction) of the porous polymer, and τ is the tortuosity.

Theories of solute diffusion through macroporous polymers assume that solute transport occurs predominantly through the water-filled pores and that this process is slowed by the available pore space for transport (ε) and by the geometric characteristics of the path (τ). Equations (5) and (6) assume a constant D_{eff} which requires that the void fraction and tortuosity do not change during the release process.

1. *Analysis of Pore Models*

A more accurate analysis of the porous structure may be presented using models and information originally developed for description of transport phenomena in porous rocks, ion-exchange resins, and catalysts. The rationale for use of physical and topological pore models in controlled release systems is that the tortuosity and void fraction may be calculated and verified by experimental techniques [20]. In addition, these models may be used to describe changing porosity due to continuous swelling of the porous medium [21–24].

The derivation of relevant equations follows that for porous media [25] used in tertiary oil recovery. Consider a planar cross-section P through the porous medium as in Fig. 2. Many short pores of varying lengths, orientation, and radii cross the planar section. To determine the total flux crossing P, consider a pore with orientation ψ (specified by the angles θ and ϕ) and let δ_ψ be the

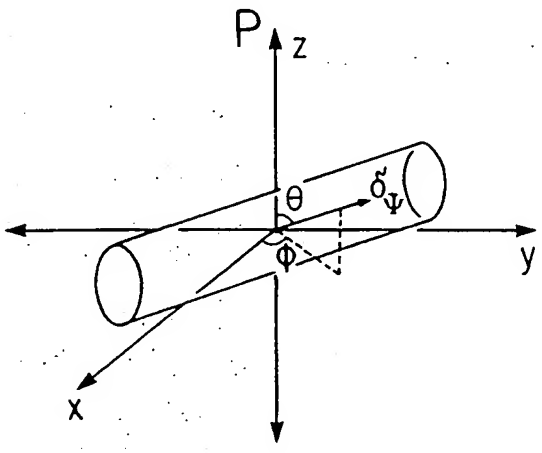

FIG. 2. Schematic representation of cylindrical pore with radius r and orientation ψ (specified by the angles θ and ϕ).

unit vector along the pore. The total flux for one solute through this pore is $J\delta_{\underset{\sim}{\psi}}$. It is assumed that J depends only on r (radius) and $\underset{\sim}{\psi}$.

To obtain the total flux across P due to all the pores, the elemental contributions of the individual pores are added, taking in account that only the void fraction of P is open for diffusion. If $n(r, \underset{\sim}{\psi})dr\, d\underset{\sim}{\psi}$ is the number of pores per unit area of P (recall that $d\underset{\sim}{\psi} = d\theta\, d\phi \sin\theta$), then

$$J = \int_r \int_{\underset{\sim}{\psi}} \delta_{\underset{\sim}{\psi}}(\underset{\sim}{\psi})\, J_i(r, \underset{\sim}{\psi}) n(r, \underset{\sim}{\psi}) dr\, d\underset{\sim}{\psi} \tag{7}$$

The function $n(r, \underset{\sim}{\psi})$ is the void fraction per interval of pore radius r.

From this analysis one obtains

$$J = -\int_r \int_{\underset{\sim}{\psi}} D_{iw} \frac{1}{f(r)} \delta_{\underset{\sim}{\psi}}(\delta_{\underset{\sim}{\psi}} \cdot \nabla c) n(r, \underset{\sim}{\psi})\, dr\, d\underset{\sim}{\psi} \tag{8}$$

Equation (8) can be written in terms of measurable parameters since the concentration is independent of r and $\underset{\sim}{\psi}$ and the pore orientation is independent of the radii of the pores.

$$J = -\int_{r=0}^{\infty} D_{iw} \frac{1}{f(r)} \underset{\approx}{\kappa}(r) \cdot \nabla c\, d\varepsilon(r) \tag{9}$$

The function $\varepsilon(r)$ is the observed void fraction of pores with radii less than r. It is defined as

$$\varepsilon(r) \equiv \int_0^r \int_{\underset{\sim}{\psi}} n(r, \underset{\sim}{\psi})\, d\underset{\sim}{\psi}\, dr \tag{10}$$

The tortuosity $\underset{\approx}{\kappa}$ is a symmetric second-order tensor and it is defined as

$$\underset{\sim}{\kappa}(r) \equiv \frac{\int_{\underset{\sim}{\psi}} \delta_{\underset{\sim}{\psi}}(\underset{\sim}{\psi})\delta_{\underset{\sim}{\psi}}(\underset{\sim}{\psi}) n(r, \underset{\sim}{\psi})\, d\underset{\sim}{\psi}}{\int_{\underset{\sim}{\psi}} n(r, \underset{\sim}{\psi})\, d\underset{\sim}{\psi}\, dr} \tag{11}$$

For isotropic porous media, $\underset{\sim}{\kappa}$ is isotropic. Then for one-dimensional diffusion one may write

$$J_i = -\int_{r=0}^{\infty} D_{iw} \frac{1}{f(r)} \frac{\partial c}{\partial z} \kappa(r)\, d\varepsilon(r) \tag{12}$$

where D_{iw} is the diffusion coefficient of the bioactive agent. The function $f(r)$ is used to express the distribution of pore radii. The tortuosity κ is exactly reciprocal to the tortuosity τ that is usually used in controlled release systems and in catalysis. Integration of Eq. (12) is done over all the "available" open space, i.e., over the volume of the pores $d\varepsilon(r)$, which depends on the magnitude of the radii.

Several simplified expressions of Eq. (12) have been proposed by Feng and Stewart [26]. The most common model assumes an isotropic porous medium with uniform porous radii where

$$J = -D_{iw}\, \varepsilon\kappa \frac{1}{f(r_1)} \frac{\partial c}{\partial z} = -D_{iw} \frac{\varepsilon}{\tau f(r_1)} \frac{\partial c}{\partial z} \tag{13}$$

with

$$D_{eff} = D_{iw} \frac{\varepsilon}{\tau f(r_1)} \tag{14}$$

In the theory of porous media the term $\varepsilon\kappa$ in Eq. (13) is known as the obstruction factor Q_m and is defined as

$$Q_m = \varepsilon\kappa = \varepsilon/\tau = D_{eff}/D_{iw} \tag{15}$$

It is obvious from the previous analysis that some of the parameters of Eqs. (12) and (13) are adjustable, namely ε, κ, and $f(r)$. However, if one knows that a controlled release system consists of a carrier polymer with pores of specific geometry and topology, one can determine transport properties. In the worst case, one

may need some data on porosity or pore-size distribution to verify which pore model is best for the system investigated.

A number of "capillary" pore models have been proposed for the calculation and prediction of the effective diffusivity [27, 28]. The porous space is conceived as a collection of differently sized capillaries, randomly oriented and connected. The effective flux relations for the porous solid are derived from the flux relations of a single capillary averaged with respect to the pore size distribution.

Haynes and Brown [29] discuss a capillary model assuming parallel pores. This model has received a great deal of recognition because of its conceptual and mathematical simplicity and its ability to predict experimental data. The parallel pore model incorporates a tortuosity factor to account for nonidealities in the porous structure. Use of a tortuosity factor of $\tau = 3$ in Eq. (6) has proven adequate in most cases for predicting effective diffusivity in commercial catalysts.

Models with some applicability to macroporous controlled release systems have been proposed [30–32]. These are series-pore models with two types of capillaries of two different radii. Their ability to predict controlled release of drugs has been tested [32]. A detailed analysis of these and other empirical models can be found in a recent review [33].

A modification of the capillary approach are random pore models. A set of capillaries is cut into elements of uniform length. The elements are rejoined with random displacements from their initial position, but they are kept aligned along the direction of microscopic diffusion [34, 35].

Network models attempt to describe the connectivity and distribution of the voids and pores of the three-dimensional network of most pore structures. Two-dimensional lattice models comprise the majority of network models [36, 37]. The mathematical intractability of three-dimensional network calculations has limited their use. Several network models have been advanced, varying in degree of complexity and application [38].

One recent approach to analyzing pore models in controlled release systems is the use of Monte Carlo techniques and percolation theory [39]. As a simple example of how the percolation theory [40] works, consider a slab of solid medium which may be divided into many identical small cells. If these solid square cells contain polymer, one starts replacing some of these cells randomly by cells of equal volume containing drug. Since this process is done randomly, at low loadings of bioactive agent a continuous path of a drug from one surface of the slab to the other may not be possible. Most probably, isolated regions of drug in the polymer are observed. Each region may consist of one, two, or three square cells, but as the polymer cells are randomly replaced by drug cells,

we approach the volume fraction of cells at which at least one "set of drug cells" will be "connecting" the two surface. Therefore, at a critical fraction, X_c, called the percolation threshold of the medium (polymer), the slab becomes a "drug-conductor" (according to percolation terminology). Mathematically, the problem of determining X_c can be solved in two-dimensional or three-dimensional fashion, using squares, triangles, or any other shape of cells of equal size [41]. Larson et al. [42] gave values of X_c for certain percolation processes.

D. Microporous Systems

Solute diffusion through microporous membranes in the absence of convection may be described by Fickian or multicomponent diffusion equations. For diffusion through micropores, the solute diffusion coefficient refers to solute diffusion through the water-filled pores. The structure of the pores in the membrane is incorporated into the diffusion coefficient by means of the void fraction (porosity) ε and the tortuosity τ. When the solute is soluble in the polymer, a pore wall partition coefficient K_p must be incorporated into the diffusion coefficient [6, 7]. Thus the final form of the diffusion form of the diffusion coefficient D_{eff} is

$$D_{eff} = \frac{D_{iw} \varepsilon K_p K_r}{\tau} \tag{16}$$

where ε is the pore volume fraction, τ is the tortuosity, K_p is the equilibrium partition coefficient, i.e., the ratio of concentration inside the pore to concentration outside the pore, and K_r is the fractional reduction in diffusivity within the pore which results when the solute diameter d_s and pore diameter d_p are of comparable size [43].

For unsteady-state diffusion in a porous solid, the variation of concentration in the pores with time is described by

$$\frac{\partial c_i}{\partial t} = D_{eff} \frac{\partial^2 c_i}{\partial z^2} \tag{17}$$

The parameter K_r of Eq. (16) depends upon the value of the ratio of molecular diameter to pore diameter. Satterfield et al. [44]

studied restricted diffusion using a variety of binary systems of hydrocarbons and aqueous solutions of salts and sugars in silica-alumina catalyst beads, for which λ ranged from 0.1 to 0.5. For solutes that did not preferentially adsorb on the porous medium, their results were well correlated by

$$\log\left(\frac{\tau D_{eff}}{D_{iw}}\right) = -2.0\lambda \tag{18}$$

In a later study using macromolecules, Colton et al. [43] found reasonable agreement between Eq. (18) and the experimental results of the effective diffusion coefficient of certain compact and relatively rigid proteins.

In the special case of microporous systems where the size of the diffusing species is of the same order of magnitude as the diameter of the pore, special simplified expressions have been developed to describe the transport process of a solute. The Faxén equation [45] may be used

$$D_{im}/D_{iw} = (1 - \lambda)^2(1 - 2.104\lambda + 2.09\lambda^3 - 0.95\lambda^5) \tag{19}$$

where

$$\lambda = r_s/r_p \tag{20}$$

and D_{im} and D_{iw} are the diffusion coefficients of the solute in the polymer and water, respectively. The radius of the solute is presented by r_s, while the radius of the pore is represented by r_p. Further corrections of this theory have been discussed by Anderson and Quinn [46], Colton et al. [43], and Satterfield et al. [44].

E. Nonporous Systems

For nonporous, homogeneous polymeric systems Fick's law (Eq. 1) may be integrated to give

$$J_i^* = \frac{D_{ip}K_i\Delta c_i}{\delta} \tag{21}$$

where the solute partition coefficient K_i describes the equilibrium ratio of the saturation concentration of the solute in the membrane

to that in the surrounding release media (e.g., water), and Δc_i represents the solute concentration difference of the solutions on either side of the membrane.

The steady state flux J_i^* per unit area of exposure A can be also expressed as dM_i/Adt, where M_i is the quantity of solute diffusion at time t. Solute diffusion rates are time-independent and can be controlled by geometric factors (thickness and surface area of the membrane) and physicochemical parameters (solute diffusion coefficient in the polymer, D_{im}, and solute partition coefficient, K_i). The last two terms are often combined as $D_{im}K_i$ or $D_{im}K_i/\delta$ to describe the membrane permeability coefficient, P_{im}. Methods of experimentally determining these parameters have been reviewed [5]. The choice of polymer determines membrane permeability and therefore diffusion rate of each solute.

Optimum diffusion conditions can be achieved by controlling the crystalline phase, porous structure, degree of swelling, additive concentration, mesh size of the cross-linked macromolecular chains, and thermodynamic transitions related to macromolecular relaxation phenomena, namely glassy/rubbery transitions in the presence of a solute and a swelling agent, usually water [13, 14]. Thermodynamic interactions between the polymer and the diffusing species are also important [7]. The nature of intensive variable gradients responsible for transport, such as chemical potential, pressure, electrostatic potential, and temperature gradients, must be investigated and controlled [47].

1. *Effect of Physical and Chemical Cross-Links*

For cross-linked or uncross-linked rubbery polymers, Fickian diffusion of the bioactive agent is observed. The solute diffusion coefficient is dependent on the equilibrium polymer volume fraction in the swollen polymer matrix, the cross-linking density, and the size of the solute. Recent theoretical analyses [9, 10, 12, 14] give the general behavior of the solute diffusion coefficient D_{im} for highly swollen polymers:

$$\frac{D_{im}}{D_{iw}} = k_1\left[\frac{\bar{M}_c - \bar{M}_c^*}{\bar{M}_n - \bar{M}_c^*}\right]\exp\left[\frac{-r_i^2 k_2}{Q-1}\right] \tag{22}$$

where D_{im} and D_{iw} are as previously defined, $\bar{M}_c$ and $\bar{M}_n$ are the number-average molecular weight between cross-links (for the

network membrane) and before cross-linking (for the original polymer chains), respectively, $\bar{M}_c^*$ is the value of $\bar{M}_c$ below which no diffusion of the solute can occur, and r_i is the characteristic radius of the solute. The swelling ratio Q is expressed as ν_2^{-1}, where ν_2 is the polymer volume fraction in a completely swollen membrane. Finally, k_1 and n_2 are constants characteristic of the system.

It is evident from this analysis that the cross-linked structure of polymer membranes creates a "screening effect" on solute diffusion through polymers even for highly swollen systems (Fig. 3). For uncross-linked polymers, this "screening" is provided by the mesh formed by entangled chains. The main mechanism of solute diffusion is through the water (solvent) regions of the membrane. Increasing the size of the solute leads to a significant decrease of D_{im}.

Moderately cross-linked solute carriers such as swollen poly(2-hydroxyethyl methacrylate) deviate from this theory. Recently Peppas et al. [48] extended the previous theories to these systems by describing the normalized solute diffusion coefficient D_{im}/D_{iw} by the following equation:

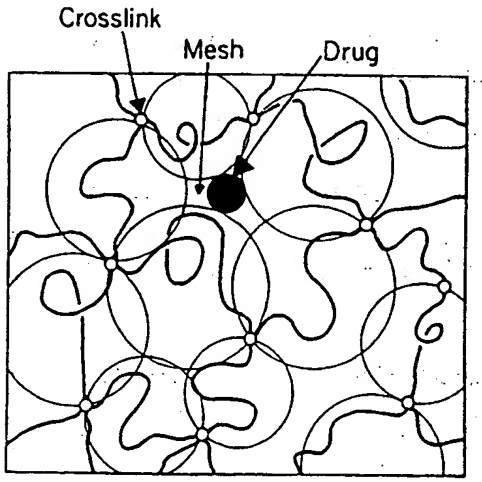

FIG. 3. Diffusional solute screening of a macromolecular network. Open circles designate chemical cross-links. Spheres around macromolecular chains define possible regions of chain fluctuations.

$$\frac{D_{im}}{D_{iw}} = k_1 \xi \exp\left[- \frac{k_2 r_i^2 \xi}{\bar{M}_n^2 (Q - 1)} \right] \tag{23}$$

The parameters used here are the same as in Eq. (22) with the exception of the mesh size, ξ, which describes the average size of the space between four tetrafunctional cross-links or four entanglements in the membrane.

2. Effect of the Crystalline Phase

In semicrystalline rubbery polymers solute diffusion is significantly slowed down by the crystallites [49]. Diffusion may still be treated as Fickian with effective diffusion coefficient D_{im}' defined as

$$D_{im}' = \psi D_{im} / \beta \tag{24}$$

where D_{im} is the diffusion coefficient in the amorphous rubbery polymer, ψ is the "detour ratio" which accounts for reduction in solute mobility due to the tortuosity of diffusion paths between crystallites, and β is an "immobilization factor" that accounts for physical cross-linking due to the crystallites [50]. The detour ratio ψ is proportional to a power of the amorphous polymer volume fraction, v_2; the value of β depends on the size of the diffusing species.

3. Macromolecular Relaxations

Diffusion of a bioactive agent through an initially glassy polymer which is placed in contact with a swelling agent may be affected by macromolecular relaxations occurring in the polymer near the glass transition temperature [51–60]. These relaxations become important at the glassy/rubbery polymer front (interface) [61] and, in turn, control the mechanism of diffusion and release of the solute [62–64].

The importance of macromolecular relaxations in solute diffusion is associated with two dimensionless numbers, the diffusional Deborah number De and the swelling interface number Sw. The Deborah number is defined according to Eq. (25), where λ is the characteristic stress-relaxation time for the polymer/swelling agent pair and θ is the characteristic time for diffusion of the swelling agent in the polymer,

$$De = \lambda/\theta \tag{25}$$

Therefore, λ and θ may be defined by Eqs. (26) and (27), where $G(s)$ is the shear-relaxation modulus [65], δ is the sample thickness, and D_s is the diffusion coefficient of the swelling agent in the polymer:

$$\lambda = \frac{\int_0^\infty sG(s)\,ds}{\int_0^\infty G(s)\,ds} \tag{26}$$

$$\theta = \delta^2/D_s \tag{27}$$

Regions of Fickian and non-Fickian (anomalous) diffusion of the swelling agent in the polymer may be defined by calculating the value of De [66, 67]. For values of De >> 1 or De << 1, diffusion is unaffected by macromolecular relaxations and Fickian diffusion should be observed. Anomalous diffusion behavior occurs when De is of the order of one. A special case of anomalous diffusion, known as Case II transport [52–55, 61], is observed when the glassy/rubbery interface moves inwards at a constant velocity.

Although macromolecular relaxations are associated also with countercurrent diffusion of incorporated bioactive agents, it is the relative mobility of the diffusing bioactive agent with respect to the penetrating swelling agent that controls the mechanism of solute release. A Peclet-like dimensionless number, the swelling interface number, may be defined according to Eq. (28), where v is the velocity of the swelling interface:

$$Sw = v\delta(t)/D_{ip} \tag{28}$$

When the rate of solute transport through the solvated region is faster than the rate of advancement of the swelling interface, Sw is much smaller than one and the bioactive agent diffuses under a Case II transport mechanism [68, 69]. General anomalous transport of the bioactive agent is observed for Sw $\simeq$ 1, whereas Fickian diffusion is observed when Sw >> 1 even if De $\simeq$ 1.

III. DIFFUSION-CONTROLLED SYSTEMS

Diffusion-controlled systems are the most widely used for delivery of bioactive agents. They comprise reservoir (Fig. 4) and matrix (Fig. 5) systems. Generally, two cases of diffusion exist for each type of system. Diffusion occurs either through the space between the macromolecular chains with diffusion coefficient D_{ip} or through a porous network filled with aqueous medium with an effective diffusion coefficient D_{eff}, incorporating both porosity and tortuosity.

In view of the previous analysis of diffusion in polymers, release of drugs through macromolecular chains may be described by Eqs. (1) and (2), whereas release through a porous carrier is described by Eqs. (5), (6) or (16), and (17).

Simplified expressions for prediction of solute release from various diffusion-controlled systems have been obtained and are widely used when describing diffusional solute release [5, 6].

A. Reservoir Systems

Reservoir diffusion-controlled systems consist of a thin membrane separating a core of bioactive agent from the biological en-

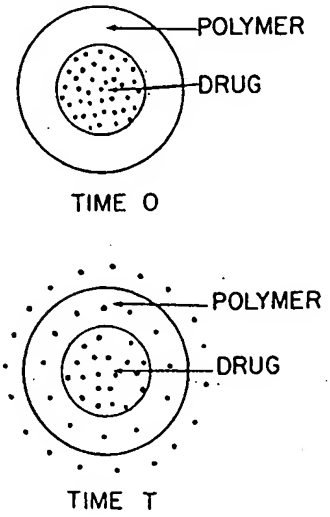

FIG. 4. Schematic diagram of a cross section of a cylindrical diffusion-controlled reservoir system.

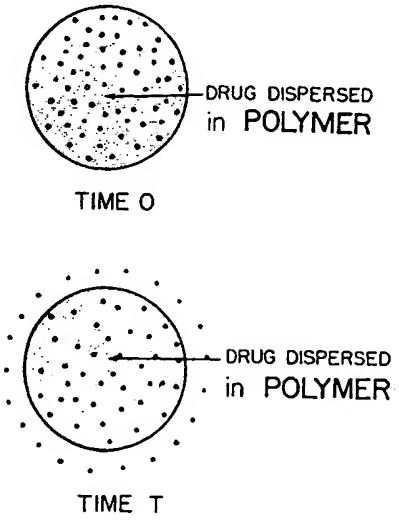

FIG. 5. Schematic diagram of a cross section of a cylindrical diffusion-controlled matrix system.

vironment (Fig. 4). For concentration-independent solute diffusion coefficient in the polymer, D_{ip}, and constant thickness, Eq. (1) may be integrated to yield

$$J_i^* = \frac{dM_i}{A\,dt} = D_{ip}\,K\,\frac{\Delta c_i}{\delta} \tag{29}$$

where K is the solute partition coefficient and A is the membrane area.

To maintain a constant flux, the transmembrane concentration difference Δc_i must be kept constant. This can be done by maintaining a constant drug concentration in the internal phase by placing excess solid drug inside the reservoir system to maintain a saturated solution of drug even as diffusion progresses. Reservoir systems exhibit nearly zero-order or time-independent diffusional solute release behavior.

Most common reservoir systems are of planar, cylindrical, or spherical geometry. Equation (1) may be solved for these systems to yield expressions of the total amount of drug released, M_i at time t. For membranes (neglecting edge effects, Eq. (29) gives

$$M_i = \frac{D_{ip} K A \Delta c_i}{\delta} t \tag{30}$$

For cylindrical devices the corresponding expression is

$$M_i = \frac{D_{ip} K A \Delta c_i}{\ln (r_e/r_i)} t \tag{31}$$

where r_e and r_i are the external and internal radius of the cylinder, respectively, and $A = 2\pi l$ is the area of the cylinder of length l. Finally, for spherical reservoir systems, Eq. (32) can be used:

$$M_i = \frac{4\pi D_{ip} K \Delta c_i}{(r_e - r_i)/r_e r_i} t \tag{32}$$

Clearly, solute release is proportional to time and can be controlled by adjusting the geometry of the device, the thickness of the membrane, the concentration difference Δc_i, the thermodynamic characteristics of the system through the partition coefficient, and the structure of the polymer through the solute diffusion coefficient as discussed in Section II.

Special diffusional release problems observed with reservoir systems include time-lag and burst effects. They are related to the time history of the device [7, 11, 47].

The time-lag effect alters the initial release kinetics of the expected time-independent release behavior due to an induction period for solution diffusion. Then the amount of solute released from membranes is

$$M_i = \frac{D_{ip} A \Delta c_i}{\delta} \left(t - \frac{\delta^2}{6 D_{ip}} \right) \tag{33}$$

The burst effect is related to solute accumulation at the membrane–water interface before the device is placed in contact with water. The solute release for systems exhibiting this phenomena is expressed by

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$$M_i = \frac{D_{ip} A \Delta c_i}{\delta} \left(t + \frac{\delta^2}{3D_{ip}} \right) \tag{34}$$

There are experimental situations where solute release from reservoir systems occurs in dissolution media of finite volume and for nonconstant activity. Baker and Lonsdale [11] have derived simple expressions which can be used for these cases.

Reservoir systems have found extensive use in medical applications. They include capsules, microcapsules, hollow fibers, liposomes, and membranes, and they have been used in ocular therapy, birth control, transdermal systems, cancer therapy, etc. Polymeric materials which have been used for these applications include a variety of hydrogels, especially poly(2-hydroxyethyl methacrylate) (PHEMA), silicone networks, and ethylene vinyl acetate copolymers (see Section III-C).

B. Matrix Systems

In matrix systems the bioactive agent, either in dissolved or in dispersed form, is incorporated in the polymer phase. Therefore, the solubility of the solute in the polymer becomes a controlling factor in the release from these systems. Mathematical solutions of Eq. (2) can be obtained for a variety of initial and boundary conditions [7, 8, 47] which represent appropriate experimental situations. Here we will concentrate on solutions applicable to diffusional solute release from slabs, although similar expressions may be obtained for other geometries.

1. Systems with Dissolved Drug

In these systems the drug is dissolved in the polymer matrix and solute diffusion can be expressed by Eq. (2). Solutions have been obtained for constant concentration of the solute at the polymer/dissolution interface. For a slab, the fractional solute release, M_i/M_∞ is

$$\frac{M_i}{M_\infty} = 1 - \sum_{n=0}^{\infty} \frac{8}{(2n+1)^2 \pi^2} \exp\left[\frac{-D_{ip} (2n+1)^2 \pi^2}{\delta^2} t \right] \tag{35}$$

A convenient simplification of this equation for short times has been used quite successfully to predict solute release from most

matrix systems. According to Eq. (36), which may be used for $M_i/M_\infty < 0.6$, the fractional release is proportional to the square root of release time, which means that the solute release rate, dM_i/dt, decreased according to a $t^{-1/2}$ dependence:

$$\frac{M_i}{M_\infty} = 4\left(\frac{D_{ip}t}{\pi\delta^2}\right)^{1/2} \tag{36}$$

This observation is important since it shows that it is not possible to obtain constant solute release rates from dissolved drug matrix systems possessing simple geometries.

Solutions for other geometries and boundary conditions have been discussed [47]. Most models for controlled-release kinetics available in the literature have been derived for boundary conditions which do not consider mass transfer limitations at the polymer/water interface.

2. Systems with Dispersed Drug

Matrix systems may contain solute originally dispersed in the polymer at a concentration c_0 which is higher than the solubility in the polymer c_{is}. The Higuchi model [70] is a pseudo-steady-state solution of Eq. (2) for this case. It predicts that the drug released, M_i, is proportional to the square root of release time according to

$$M_i = A[D_{ip}c_{is}(2c_0 - c_{is})t]^{1/2} \tag{37}$$

Exact solutions of this model have been presented by Paul and McSpadden [71], without the assumption of pseudo-steady state, by treating the phenomenon as a moving boundary problem. The solute release is expressed by

$$M_i = \frac{2c_{is}A}{\operatorname{erf}\left(\dfrac{x^*}{2\sqrt{D_{ip}t}}\right)}\left(\frac{D_{ip}t}{\pi}\right)^{1/2} \tag{38}$$

where x^* is the position of the continuously dissolving drug, which may be calculated from the following transcendental equation:

$$x^*\left(\frac{\pi}{D_{ip}t}\right)^{1/2} \exp\left(\frac{x^{*2}}{4D_{ip}t}\right) \operatorname{erf}\left(\frac{x^*}{2\sqrt{D_{ip}t}}\right) = \frac{c_{is}}{c_0 - c_{is}} \tag{39}$$

Approximate and numerical solutions of similar moving boundary problems of diffusional drug release under various boundary conditions have also been presented by Lee [72] and Korsmeyer and Peppas [64]. As in the systems with dissolved drug, release rates decrease with time for devices possessing a simple geometry, such as a slab. However, specially shaped devices which display increasing drug availability as the distance from the surface increases (e.g., a hemisphere coated on all surfaces except for a small cavity in the central face (Fig. 6)) do exhibit zero-order release [73].

3. Porous Matrix Systems

As discussed before, in porous matrix systems diffusional solute release is controlled by the dissolution of the drug and by its diffusion through the water-filled pores. Under these conditions Eq. (17) must be solved under appropriate boundary conditions.

The pseudo-steady-state model for these systems [74] predicts solute release according to

$$M_i = A[D_{eff}c_{is}(2c_0 - \varepsilon c_{is})t]^{1/2} \tag{40}$$

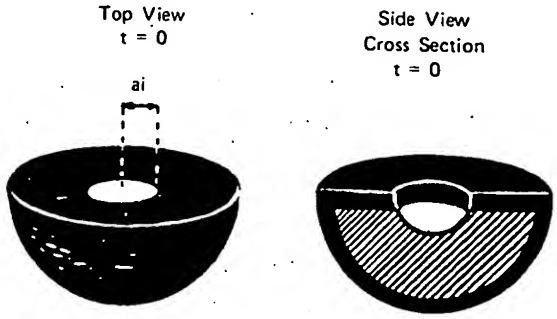

FIG. 6. Schematic diagram of a hemispheric matrix system that is coated on all surfaces with an impermeable coating (black) except for an aperture in the center face. The shaded region is the polymer–drug mixture. The geometric design of this device results in zero-order release rates [73].

Two alternative models have been recently discussed [75, 76]. An exact solution of Eq. (17) without the pseudo-steady-state approximation has been obtained in the form of

$$M_i = \frac{2\varepsilon^{2/3} c_{is} A}{\operatorname{erf}\left(\frac{x^*}{2\sqrt{D_{iw}'t}}\right)} \left(\frac{D_{iw}'t}{\pi}\right)^{1/2} \tag{41}$$

where x^* is the position of the front determined from the following transcendental equation:

$$x^* \left(\frac{\pi}{D_{iw}'t}\right)^{1/2} \exp\left(\frac{x^*}{4D_{iw}'t}\right) \operatorname{erf}\left(\frac{x^*}{2\sqrt{D_{iw}'t}}\right) = \frac{c_{is}}{\rho_i - c_{is}} \tag{42}$$

where ρ_i is the density of solid drug and D_{iw}' is a normalized solute diffusion coefficient in water which is defined according to

$$D_{iw}' = D_{iw}/\tau \tag{43}$$

The second approach is based on a diffusion/dissolution model which incorporates drug dissolution as a rate-limiting step during the early phase of diffusional release [76].

C. Polymers for Diffusion-Controlled Systems

Major categories of polymeric materials which have been used for development of reservoir and matrix-type, diffusion-controlled delivery systems include water-swollen, cross-linked, polymeric networks (hydrogels) of homo- and copolymers, silicone networks, and ethylene–vinyl acetate copolymers. Their common characteristics include chemical and physical stability, biological inertness, and processability. These polymers have been used as integral components of systems approved by the Food and Drug Administration. In addition, numerous sustained release systems have been prepared from cellulose derivatives, including conventional tablets. Ethylcellulose and hydroxypropylcellulose are the most common grades of cellulose derivatives for these formulations.

1. Swollen Cross-Linked Hydrophilic Networks (Hydrogels)

Poly(2-hydroxyethyl methacrylate) (PHEMA) is a hydroxylated polymethacrylate prepared by polymerization of the monomer HEMA in the presence or absence of water or other polar solvents and in the presence of a small quantity of cross-linking agent [77–81]. The most commonly used cross-linking agent is ethylene glycol dimethacrylate (EGDMA) although other cross-linking agents such as tri- and tetraethylene glycol dimethacrylate have also been employed [82, 83]. Typical initiators include benzoyl peroxide and azobisisobutyronitrile; reaction temperatures vary from 50 to 90°C. The reaction is a copolymerization/cross-linking process and the cross-linking agent is usually added in concentrations of less than 1 wt%.

The earliest work on PHEMA hydrogels was reported by Wichterle and Lim [84]. Extensive research has been done on the thermodynamic properties and swelling behavior [85–88], mechanical properties [89–91], diffusion behavior [83, 92–94], and application of these hydrogels [77, 78, 95]. Other monomers which have been discussed for preparation of polymers for controlled release applications include hydroxyethoxyethyl methacrylate (HEEMA), hydroxydiethoxyethyl methacrylate (HDEEMA), and the methoxy-derivatives thereof [81]. Copolymers of HEMA and HEEMA with N-vinyl-2-pyrrolidone (NVP), methacrylic acid, and methyl methacrylate (MMA) have also been used [77].

The equilibrium degree of swelling of these systems varies from 10 to 95% depending on their structure, hydrophilicity, and degree of cross-linking [77, 81]. Despite their high content of water, these systems may be used for the release of both hydrophilic and hydrophobic drugs [96].

PHEMA and related cross-linked homopolymers and copolymers have been used for the release of progesterone from rod-shaped matrix-type systems [97] exhibiting first-order release behavior. Fluorine-containing inorganic salts can be released from copolymers of HEMA and MMA for dental applications [98]. Applications in induction of therapeutic abortion using release of prostaglandins, PGE_2 and $PGF_{2\alpha}$, from PHEMA matrix systems have been discussed [99]. Release of tripelennamine-hydrochloride from cross-linked PHEMA devices was investigated [100]. More recent applications of hydrogels based on hydroxylated methacrylates have included the release of heparin for anticoagulation [101] and the release of phenformin-hydrochloride, an oral antihyperglycemic drug [102].

Multilayered devices consisting of cross-linked HEMA copolymers were recently reported [103]. These systems consist of a core polymer with drug dissolved in it which is surrounded by layers of polymer of progressively increasing degrees of cross-linking.

Using a two-layered system, quasi-zero-order release of progesterone for up to 60 d was achieved.

Other hydrogels with potential controlled release applications include cross-linked poly(vinyl alcohol) (PVA) and its copolymers especially with NVP. PVA is prepared by polymerization of vinyl acetate and subsequent hydrolysis of the ensuing polymer. Cross-linking is achieved by chemical or irradiative techniques. These cross-linked networks can be swollen by water up to 90% and their thermodynamic, swelling [104–109], mechanical [104], and diffusion behavior [9, 10] is well established. Copolymers with NVP have been discussed [110]. PVA matrix systems have been used to release theophylline, albumin, and other molecules at rates which in most cases are controlled by the degrees of cross-linking and crystallinity [13, 14, 24, 47].

Hydrogels have also been used to release narcotic antagonists [111] and antibiotics [112].

2. *Silicone Networks*

Polydimethylsiloxanes (PDMS) and related silicone-containing polymers have been used for controlled release of hydrophobic drugs. They are prepared by polymerization of linear silanols and can be cross-linked by benzoyl peroxide or other cross-linking or coupling agents. Folkman et al. [113] used these materials for release of anesthetics; Roseman [114] established the importance of the partition coefficient of drugs in the polymer as a means of controlling the release rate. Several other pharmaceutical applications have been described [115–117].

3. *Ethylene–Vinyl Acetate Copolymers*

Ethylene–vinyl acetate (EVAc) copolymers have found major applications in controlled release of bioactive agents because of their relatively good chemical stability, biocompatibility, and inertness [118]. They are prepared by copolymerization of ethylene and vinyl acetate [119, 120] and are sometimes cross-linked by peroxides [120]. They are rubbery materials with two glass transition temperatures, depending on the vinyl acetate content and they may have also a low content of crystalline phase depending on the condition of preparation. Typical EVAc copolymers used for controlled release applications contain 30–50 wt% vinyl acetate. The solubility behavior of several solvents in EVAc has been discussed [121].

Ethylene–vinyl acetate copolymers are the rate limiting barriers in several controlled release reservoir devices including the Ocusert, which releases pilocarpine over a one-week period to glaucoma patients [122], and the Progestasert, which releases progesterone

for over one year to aid in birth control [123]. These polymers have also been used in transdermal systems.

Ethylene–vinyl acetate copolymers have also composed the polymer matrix for diffusion-controlled systems that release macromolecules such as proteins [124]. By solvent casting powdered macromolecular drugs in a solution of ethylene–vinyl acetate copolymer, a series of tortuous interconnecting pores are formed in the normally nonporous polymer [125]. Those pores are large enough to permit the diffusion of macromolecules. The pore structure is affected by the size of the particles and the loading (weight percentage of the matrix that is drug); these parameters can be used to regulate the release rates of macromolecules from these polymers [126].

IV. CHEMICALLY-CONTROLLED SYSTEMS

Chemically-controlled drug release generally involves one of two types of systems: 1) Erodible systems in which the drug is dispersed in a biodegradable polymer and drug release is influenced by the rate of degradation of the polymeric material (Fig. 7), and 2) pendant chain systems in which the drug is attached to a polymer through a hydrolytically or enzymatically labile linkage. Drug release is influenced by the rate of degradation of this

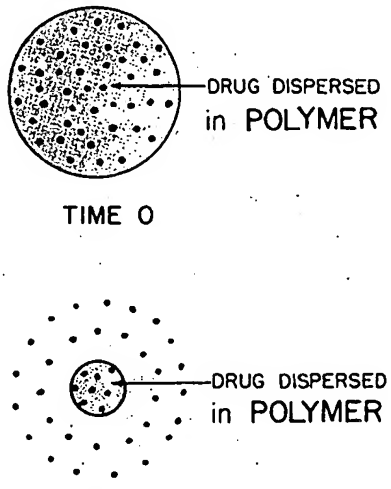

FIG. 7. Schematic diagram of a cross section of surface-eroding bioerodible system.

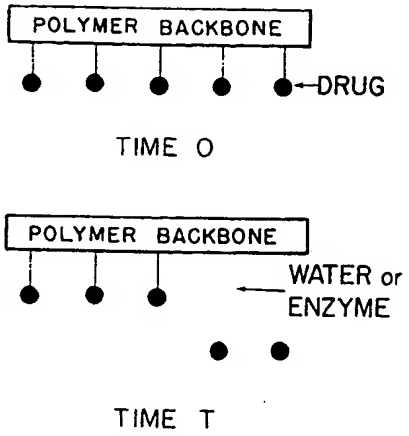

FIG. 8. Schematic diagram of a pendant chain system.

linkage (Fig. 8). In both cases it is more desirable to have the degradation process hydrolytically—rather than enzymatically—controlled since there is little patient to patient variation in water concentration.

A. Erodible Systems

Erodible systems may also be called degradable or absorbable systems. Both reservoir and matrix devices can be used. The rate of drug delivery from reservoir devices that have a rate-controlling bioerodible membrane surrounding a drug core is constant and predictable provided the membrane erodes long after drug delivery has been completed. If the rate-controlling membrane erodes significantly during drug delivery, changes in membrane thickness or physical properties would be reflected in changes in drug delivery rate. Thus, in this type of device the rate of drug release can be controlled by changing the nature of the bioerodible membrane; bioerosion serves to remove the expended device.

Drug release from matrix devices can be controlled by either diffusion or erosion. If erosion of the matrix is much slower than diffusion, the release kinetics can be described as in Section III. If, however, the drug is immobilized in the matrix so that diffusional release is minimal compared to erosion, the rate of drug release will be erosion controlled. Physically, there are two general erosion mechanisms—heterogeneous and homogeneous erosion [127]. Heterogeneous erosion occurs when degradation takes place

only at the surface of a polymer matrix (surface erosion), whereas homogeneous erosion is the result of degradation occurring through the polymer matrix. The dominant erosion mechanism can be predicted from polymer hydrophobicity and morphology. Hydrophobic polymers are more likely to erode heterogeneously since water is excluded. Since hydrophilic polymers absorb water, homogeneous erosion will be favored. Superimposed on the polymer hydrophobicity is the polymer morphology. Most polymers are semicrystalline with crystalline domains separated by amorphous regions. The crystalline regions exclude water so more crystalline polymers tend toward heterogeneous erosion.

Heterogeneous or surface erosion is much more desirable because 1) it can lead to zero-order drug release provided diffusional release of the drug is minimal and the overall surface area of the device remains constant; 2) release rate is independent of the chemical and physical properties of the drug; 3) release rate can be varied simply by varying loading, making the device easy to design; and 4) mechanical integrity is maintained because erosion is confined to the matrix surface. For a device displaying heterogeneous erosion, the dependence of rate on time is a function only of surface area [128]. For cylindrical, spherical, and slab matrices, displaying heterogeneous erosion the following relationship is applicable:

$$M_t/M_\infty = 1 - [1 - k_0 t/c_0 r]^n \qquad (44)$$

where M_t is the amount of drug released from the device in time t, M_∞ is the total amount of drug released when the device is exhausted, k_0 is the erosion rate constant, t is time, c_0 is the uniform initial concentration of drug in the matrix, and r is the radius for the sphere and cylinder or the half-thickness for a slab; $n = 3$ for a sphere, $n = 2$ for a cylinder, and $n = 1$ for a slab. The model assumes that the release kinetics are not influenced by time-dependent diffusional resistances internal or external to the eroding matrix. In other words, the actual erosion process is the rate-limiting step. The model also ignores edge effects. From Eq. (44), the only geometry which gives zero-order (i.e., constant) drug release is the slab where $n = 1$. Both a sphere and cylinder result in release rates which decrease with time.

Cooney [129] performed a more detailed analysis of spheres and cylinders undergoing heterogeneous erosion. He found that, as the ratio of initial cylinder length to diameter (L_0/d_0) approached

zero and the geometry became a flat disk, the theoretical drug release rate was zero-order. As expected, the flat disk gave the same result as a slab did in Eq. (44). Cooney also modeled spheres and cylinders with bores. Solution of the equation for cylinders with a concentric bore and coated ends showed zero-order kinetics. In addition, Cooney has proposed some novel matrix shapes which can achieve zero-order release kinetics [129].

Chemically, there are three mechanisms for polymer erosion [127]: I) degradation of cross-links freeing polymer chains from the bulk matrix; II) solubilization of water-insoluble polymers as a result of hydrolysis, ionization, or protonation of a side-group; and III) degradation of labile backbone bonds to produce low molecular weight, water-soluble molecules. These are idealized mechanisms; situations in which combinations of these mechanisms operate may also occur.

Systems displaying Type I erosion generally swell and quickly release water-soluble drugs [127]. However, Type I erosion systems may be useful for drugs with low water solubility or macromolecules which can be physically entangled in a cross-linked matrix so that they cannot easily diffuse outward. Examples include the release of highly water-insoluble hydrocortisone from gelatin cross-linked with formaldehyde [130] and the release of proteins from cross-linked hydrogels based on poly(acrylamide) or poly (*N*-vinyl pyrrolidone) and poly(*N*,*N*-methylene bisacrylamide) [131]. However, in both cases release rates decrease with time since diffusion is, in general, rate-limiting; in addition, erosion rates are extremely slow.

In systems based on Type II erosion, water-insoluble polymers are solubilized by a reaction of a pendant group. This can be hydrolysis, ionization, or protonation. In this type of erosion the only reaction is solubilization and there is no significant change in molecular weight. Consequently, such polymers are not generally useful for systemic applications because of difficulty in eliminating such molecules. These polymers may be useful, however, in topical or oral application.

The major emphasis for the development of these polymers has been enteric coatings. These coatings are designed to be insoluble in a certain pH environment, usually the stomach, and to then dissolve abruptly in an environment of a different pH, such as the intestine. Usually these polymers are applied to pills as protective coatings to prolong release but do not produce steady sustained release of therapeutic agents. Heller has reviewed the properties of polymers displaying Type II erosion [127].

In systems based on Type III erosion, high molecular weight, water-insoluble polymers are converted to small, water-soluble molecules by cleavage of labile bonds in the polymer backbone.

Because these polymers are converted to small, water-soluble molecules, these systems are most useful for systemic administration of therapeutic agents from subcutaneous, intramuscular, or intraperitoneal implantation sites. It is essential that the degradation products of these polymers be completely nontoxic. Examples of these polymers are discubsed below.

1. *Polylactic Acid, Polyglycolic Acid, and Lactic/Glycolic Acid Copolymers*

The most commonly used bioerodible polymers are polylactic acid (PLA), polyglycolic acid (PGA), and lactic/glycolic acid copolymer. The successful use of these polymers as sutures and their FDA approval for this application has motivated researchers to investigate their applicability in drug delivery systems [132]. Lactic acid is a naturally occurring product of glycolysis [133] and PLA and PGA are eventually metabolized to CO_2 and water. PLA has been classified as minimally toxic [134]. There have been numerous studies and reports on the biocompatability of these homo- and copolymers [134–139].

Polymers and copolymers of lactic and glycolic acid can be polymerized directly by a polycondensation mechanism. This synthetic method is limited to lower molecular weights so the preferred method is catalytic ring-opening polymerizations of the corresponding cyclic dimers: L(−)-lactide, D(+)-lactide, and glycolide [140–143].

Poly(D(−)-lactic acid) ((−)PLA) or poly(L(+)-lactic acid) ((+)PLA) are semicrystalline (37%), isotactic, tough with a melting temperature (T_m) of 180°C, and a glass transition temperature (T_g) of 57°C. Poly(DL-lactic acid) (PLA) is completely amorphous, atactic, tough, inelastic, and has a T_g of 57°C. Poly(glycolic acid) (PGA) is semicrystalline (46–52%), tough, and inelastic with a T_m of 230°C and a T_g of 36°C [140, 144]. The copolymer using PLA instead of (+)PLA is amorphous from 0–70 mol% glycolide [140].

The *in vitro* degradation mechanism of PGA sutures has been explained in terms of a microfibrillar model. Crystalline and amorphous regions alternate along the fiber axis and polymer chains pass between the regions (called tie-chains). The interconnecting tie-chains transmit tensile loads to the crystalline regions. PGA eroded homogeneously but not at the same rate throughout the whole system. It was proposed that hydrolysis began in the amorphous regions where water could most easily penetrate. The backbone ester linkages in the tie-chain fragments which passed through the amorphous regions were hydrolyzed.

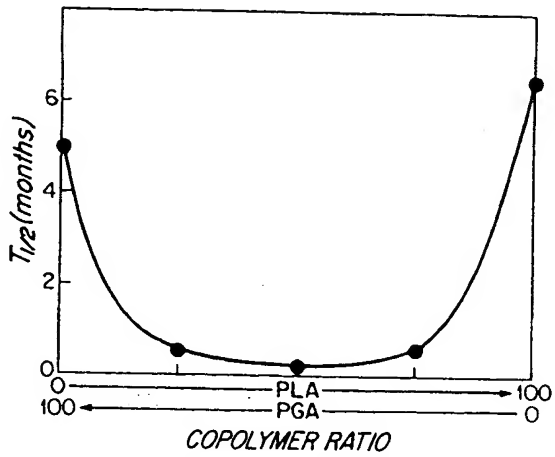

FIG. 9. Half-life *in vivo* for poly(L(+)-lactic acid-*co*-glycolic acid). Samples were implanted in rat tissue [146].

This reduced the degree of entanglement and allowed undegraded chain segments in the amorphous region to rearrange into a crystalline structure. The maximum crystallinity measured during degradation was 52%; apparently hydrolysis of crystalline regions (which occurred more slowly) began before the amorphous areas were fully eroded. Hydrolysis of the amorphous regions dominated for the first 21 d. Tensile strength was lost continuously and was completely gone (all tie chains cleaved) after 49 d. At 60 d, about 50% of the polymer was degraded yet the gross morphological shape of the suture was still unchanged [145].

The relative degradation rates *in vivo* of (+)PLA/PGA copolymers are shown in Fig. 9. The graph shows that the half-life of the implanted pellets quickly dropped from 5 months for PGA to about 1 week for a 50:50 (+)PLA/50 PGA copolymer, and increased sharply to over 6 months for (+)PLA. The polymer molecular weights were similar (MW about 40,000 to 80,000) and no preferential hydrolysis of glycolide or lactide units in the copolymers was observed [146].

The degradation of poly(DL-lactic acid) (PLA) also has been studied. Pitt and co-workers [147] observed homogeneous erosion *in vivo*. Degradation by random chain scission occurred at an even rate throughout the sample since it was uniformly amorphous. Mass loss began at a number-average molecular weight of about 15,000 and was accompanied by an increase in hydrolysis rate [147]. Homogeneous erosion at a similar rate has been observed *in vitro* as well [141] which implies the degradation process is nonenzymatic [147]. Mason and co-workers [143] calculated rate

constants for the first stage of PLA degradation in various media and at different temperatures. PLA erosion rate increased in blood where absorption of lipids may have acted as plasticizers which increased chain mobility [143].

The erosion of a series of poly(DL-lactide-co-L-lactide) (PLA/(+)PLA) and PLA/PGA polymers have been investigated by Gregory and co-workers [148] who reported an approximate ranking of erodibility, in the order of most rapid hydrolysis: 75 PLA/25 PGA > 75 (+)PLA/25 PGA > 90 PLA/10 PGA > 50 PLA/50 (+)PLA > PLA > (+)PLA.

The homo- and copolymers of lactic and glycolic acids were first applied to controlled drug release in the early 1970s [149, 150]. Since then, many different formulations have been used for bioerodible drug delivery systems [132, 151]. Several of these formulations and their drug delivery mechanisms are discussed below.

Yolles and co-workers [152] have formulated films by solvent casting polymer/drug solutions and then melt-pressing the dried cast material. In some studies the films were cryogenically ground to form polymer/drug particles [152]. Wise and collaborators formulated particles directly from cast films [153]. Pitt and co-workers formed thin films simply by solvent casting. When thicker matrixes were desired, two or three of the thinner films were stacked and melt-pressed [154]. Yolles made spherical matrixes (beads) by adding an aqueous solution of dispersing and wetting agents to an organic polymer/drug solution under strong agitation [155]. Beads were formed by Wise by molding cast films. He also formulated cylindrical matrixes (rods) by extruding cast films [137]. Matrices have been modified by dip-coating in pure polymer solutions [137], sandwiching polymer/drug films between polymer films [138], and annealing [155]. Drug delivery devices also have been formulated by microencapsulation [156] and spray drying [153].

Yolles and co-workers [157] have studied the release of contraceptive steroids, narcotic antagonists, and anticancer agents from films, beads, and particles of (+)PLA. For example, cyclazocine release *in vitro* and *in vivo* from (+)PLA (MW 70,000) films (4 cm^2 × 0.04 cm) containing 20 wt% drug and 5 wt% tributyl citrate (a plasticizer) is shown in Fig. 10. Lower polymer molecular weight (45,000) did not alter *in vivo* release rates significantly even though the polymer was observed to degrade faster [138].

Wise and co-workers [137] have investigated the *in vitro* and *in vivo* release of naltrexone and naltrexone pamoate from 75 (+)PLA/25 PGA, 90 (+)PLA/10 PGA, and (+)PLA. They identified many parameters that influence delivery rates. The results of their studies using rods and beads gave a relative naltrexone re-

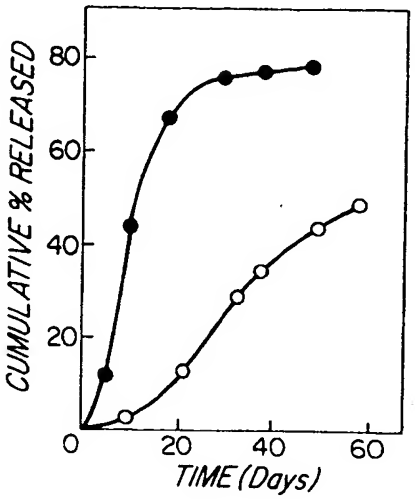

FIG. 10. Cyclazocine release form (+)PLA films (•) *in vivo* (implanted in rats), (○) *in vitro* [138].

lease rate as a function of polymer composition of 75 (+)PLA/25 PGA > (+)PLA > 90(+)PLA/10 PGA. Drug solubility in aqueous solutions was inversely related to *in vivo* release rate; the less water-soluble naltrexone pamoate was delivered more slowly than naltrexone. Also, at a given water solubility, increased drug solubility in the polymer decreased the drug release rate. In rods, the drug loading between 50 and 80 wt% was proportional to the *in vitro* drug release rate. Dip-coating beads and rods with pure polymer solutions reduced release rates both *in vitro* and *in vivo*. Wise hypothesized that drug release was the result of a combined diffusion and erosion mechanism [137]. A second study (Fig. 11) measured the affect of polymer molecular weight on sulphadrazine release *in vitro* from 1.5 mm diameter beads of 50 PLA/50 (+)PLA [158]. A further study correlated *in vitro* levonorgestrel release to the hydrolytic instability of the polymer used [148]. In an *in vivo* investigation, Wise and co-workers [159] formulated cylindrical matrixes of 90 (+)PLA/10 PGA containing 33 or 50 wt% levonorgestrel and 50 PLA/50 (+)PLA containing 50 wt% drug. Release rates fluctuated although there were periods of zero-order release. The recovered rods were brittle and encapsulated by tissue [159]. Tissue encapsulation may mask the actual behavior of controlled delivery devices *in vivo* since an aqueous boundary layer forms around the device. Drug transport across the boundary layer becomes the rate limiting step resulting in apparent zero-order kinetics [160].

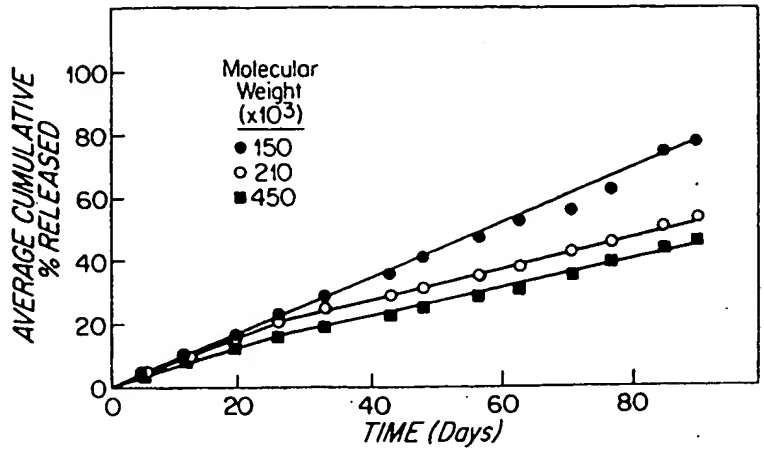

FIG. 11. Sulfadrazine release from 50 PLA/50 (+)PLA beads. Curves show effect of different molecular weight copolymers on *in vitro* release rates [158].

Pitt and co-workers [154] have studied progesterone release from films of PLA and PLA/PGA or a thin (3 μm) drug/PLA film sandwiched between two drug-free PLA films (3 μm). Ideal diffusion controlled kinetics were observed both *in vitro* and *in vivo*. A thicker, unsandwiched film (100 μm) of PLA with 10 wt% progesterone showed erratic release rates *in vitro* and *in vivo* implying leaching and/or polymer erosion were complicating drug release. Release duration was 9 weeks *in vitro* and 15 weeks *in vivo*. In films (100 μm) of about 80 PLA/20 PGA with 10 wt% progesterone, drug was initially released *in vitro* by diffusion at a very slow rate followed by a sudden increase in rate. The sudden increase coincided with the mechanical deterioration and fragmentation of the films which was probably caused by polymer hydrolysis and resulted in the exposure of more surface area [154].

Apparently, all of the above systems release drugs by diffusion or more commonly diffusion coupled with erosion. Since the homo- and copolymers of lactic acid and glycolic acid are hydrophilic and erode homogeneously, coincident diffusion and erosion would be expected. The complexity of the latter mechanism makes it difficult to predict the delivery rates. An attempt to model mixed diffusion and erosion drug release has been made by Heller and Baker [161]. This model assumes that drug release is primarily by diffusion and that homogeneous first-order polymer chain cleavage results in an increase in matrix permeability. The following equation was proposed for a film:

$$\frac{dM_i}{dt} = \frac{A}{2}\left[\frac{2P_0 \exp(Kt)c_0}{t}\right]^{1/2} \quad (45)$$

where M_i is drug released at time t, P_0 is the initial permeability of the polymer to the drug, A is the surface of both sides of the film, c_0 is the initial concentration of the drug in the polymer, and K is the first-order rate constant. The integrated form of Eq. (45) and the model for pure diffusion are shown in Fig. 12. The diffusion curve shows the expected decline in release. The polymer permeability increases in the case of both erosion and diffusion so that the normal decline in release rate is slowed and then followed by an increase in release rate analogous to reported experimental results [154]. One limitation to the model is that polymer chains in PLA films are cleaved at first-order kinetics only up to a limiting molecular weight of 5000 [147] rather than for the whole erosion process as assumed by Heller and Baker.

2. Poly(ε-caprolactone)

The main advantage of poly(ε-caprolactone) is that the permeation rates of many steroids through the polymer are very high and are similar to the rates through silicone rubber which has been widely studied for inert controlled-release devices [162]. For example, poly(ε-caprolactone) is about 10,000 times more permeable

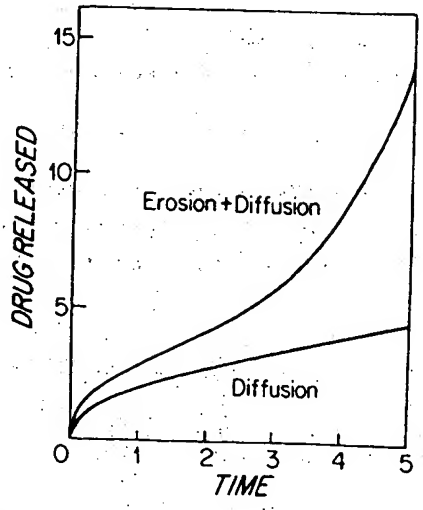

FIG. 12. Theoretical curves of drug release for a polymer slab by diffusion, and diffusion with erosion [161].

to progesterone than poly(DL-lactic acid) [144]. Thus, this polymer or copolymers of it and DL-lactide may be most useful in reservoir devices where release occurs by diffusion with erosion following.

Poly(ε-caprolactone) is synthesized by catalytic ring-opening polymerization [163]. The polymer is crystalline (45–60%) [162], tough, and flexible, T_M = 63°C [144]. Poly(ε-caprolactone) hydrolyzes to ε-hydroxycaproic acid [148]. The polymer demonstrated no adverse tissue reaction in organ and cell cultures (*in vitro*) or rat muscle tissue (*in vivo*) [134].

A homogeneous erosion mechanism was assumed for the *in vivo* degradation of poly(ε-caprolactone) since a tenfold increase in the surface area to volume ratio did not affect the rate of degradation [141]. Weight loss began once a limiting molecular weight, M_n, of about 5000 was reached [147]. Degradation was accompanied by a slow increase in crystallinity (e.g., 45 to 58% in 220 d [154]) as a result of preferential random chain cleavage in the amorphous regions of the polymer and crystallization of the resulting unrestrained tie segments [147]. (Surface erosion was also observed to occur preferentially in amorphous regions [141]). The increased crystallinity also reduced the water permeability of the polymer sample and slowed the rate of chain cleavage and weight loss [147]. The observation of similar degradation rates *in vitro* and *in vivo* suggests that enzymatic activity is not responsible for matrix breakdown [144]. Copolymers of ε-caprolactone and DL-lactide have shown a similar but more rapid erosion process. The increased rate of erosion was apparently due to reduction in crystallinity and T_g rather than a preferential erosion of one monomer over the other [147].

Capsules of poly(ε-caprolactone) and its copolymer with DL-lactide have been prepared from melt extruded polymer tubing or from polymer film rolled around a Teflon core and annealed. The tubing ends were heat sealed with warm pliers. Progesterone, testosterone, or norgestrel were micronized and dispersed in a vehicle (e.g., sesame seed oil) before being placed in the capsules. Capsule thickness was typically about 500 μm [154].

Release rates at 37°C were predicted from permeabilities of poly(ε-caprolactone) films measured in a diffusion cell. Actual release rates *in vitro* quickly decreased from the predicted levels over the first 20 d followed by a slower decline in rate over the remaining 100–200 d. The initial decline was due to changes in the dissolution rate of the dispersed drug in the seame oil. The slower, long-term decrease was due to the increase in crystallinity of poly(ε-caprolactone) as a result of polymer hydrolysis. The increased crystallinity reduced the polymer's permeability to the steroids [154].

Pitt and co-workers have also studied *in vivo* and *in vitro* progesterone (10, 20, and 30 wt%) release from films (100–300 μm in thickness) of poly(ε-caprolactone) and its copolymers with DL-lactide or glycolide. Steroid release was diffusion controlled and complete within 24 h due to high drug permeability through the polymers. No erosion effects were observed. Drug release was faster from melt-pressed films than solvent-cast films [154].

3. *Polyamides*

A number of synthetic and natural biodegradable polyamides have been reported [164–168]. For example, Sidman and collaborators have developed a copolymer of glutamic acid and λ-ethyl-L-glutamate synthesized by selective alkaline hydrolysis of poly(λ-ethyl-L-glutamate) [169]. The polymer is hydrophilic and water absorption increases with the molar fraction of glutamic acid up to about 50 mol% beyond which the polymer is water soluble [170].

The degradation mechanism of the copolymer involved two stages. Initially the ethyl ester side chains were hydrolyzed to form a water-soluble copolymer (about 45 mol% glutamic acid). This copolymer diffused away from the implant in the second step. The degradation rate increased with increasing glutamic acid content. This was probably a combination of increasing water absorption and fewer ethyl ester groups that needed to be hydrolyzed before the copolymer solubilized.

Poly(λ-ethyl-L-glutamate-*co*-L-glutamic acid) appears to be biocompatible since the dissolved copolymer was absorbed by organs such as the liver and kidney where it was enzymatically degraded to the naturally occurring L-glutamic acid. Ethanol also was a hydrolyzate [170].

This polymer has been used in matrix and reservoir systems [170]. Cylindrical matrixes (0.12 or 0.24 cm diameter) were prepared by extruding a paste consisting of 45% polymer, 45% norgestrel or progesterone (low water solubility), and 10% tetrahydrofuran (THF). The extruded cylinders were dried to remove the THF. Capsules were prepared from tubes and caps made by dip-coating glass mandrels in polymer solutions. An extruded rod of naltrexone (high water solubility) and sesame seed oil was inserted into the tubes which were capped and sealed with polymer solution. The capsules were 50 μm thick.

Permeabilities were measured at 37°C for various drugs through poly(λ-ethyl-L-glutamate-*co*-L-glutamic acid) films, and the general trends were that drugs with higher water solubilities had higher permeabilities. Permeation rates increased for all drugs as water content (as a result of higher percentages of glutamic acid in the copolymer) of the films increased. The same trend was ob-

served for *in vivo* naltrexone release from capsules. Release from matrices was affected by the low permeability of animal tissues to drugs of low water solubility. The passage of drug through the tissue proved to be rate limiting rather than diffusion of drug from the matrix or polymer erosion [170].

4. Poly(orthoesters)

In order to achieve heterogeneous rather than homogeneous erosion, it was considered necessary to synthesize hydrophobic rather than hydrophilic polymers. Ideally, hydrophobicity would prevent water from entering the interior of the polymer matrix. Poly(orthoesters) have been considered for this approach since they can be made hydrophobic but still have water labile linkages. Poly(orthoesters) are synthesized by the addition of a diol to a diketene acetal using an iodine/pyridine catalyst [171]. When 1,6-hexanediol is combined with 3,9-bis(methylene)2,4,8,10-tetraoxaspiro[5,5]undecane, the result is the formation of a linear, high molecular weight (228,000) polymer. This poly(orthoester) is hydrolytically stable in basic solutions; hydrolysis is catalyzed by the presence of acids [172].

Polyorthoesters can also be synthesized from a polyol and orthoester or orthocarbonate (Alzamer). This poly(orthoester) is hydrophobic and demonstrates the same relationship to solution pH as the previous poly(orthoester). Changes in the monomer structure permit Alzamer's with a range of physical properties to be prepared ranging from tough and glassy to soft and compliant [173]. The polymers reportedly eroded heterogeneously [173, 174] although no data on their erosion profile have been published. It has been reported that the Alzamer and its hydrolyzate induced no adverse tissue or systemic effects [173] although no data were presented.

Heller [172] prepared matrix devices containing norethindrone using the poly(orthoester), 3,9-bis(methylene)2,4,8,10-tetraoxaspiro[5,5]undecane/1,6-hexanediol. The poly(orthoester) was heated to softening and micronized sodium carbonate (10 wt%) and norethindrone (10–20 wt%) were mixed in with Teflon paddles. The sodium carbonate (a basic salt) was added to buffer the interior of the matrix to prevent homogeneous degradation. Since the poly(orthoester) is stable under basic conditions, polymer hydrolysis is limited to the matrix surface where the basic salt is neutralized by the external physiological buffer. The drug, salt, and polymer mixture were melt pressed into sheets using Teflon-coated foil and shims. Disks of 0.63 cm diameter were punched from the melt-pressed sheets and erosion studies were conducted at 37°C in 0.1 *M* phosphate buffer (pH 7.4) [172].

Heller's data showed norethindrone release to be zero order. An investigation of the release mechanism, however, demonstrated that the release was not a result of heterogeneous matrix erosion. Heller suggested that once the disk was placed in an aqueous environment, water began to diffuse into the matrix. When water contacted the sodium carbonate embedded in the matrix close to the surface, the salt dissolved. Heller suggested that this dissolved salt exerted an osmotic pressure causing the polymer to imbibe more water; the matrix swelled and drug was released by diffusion. The basic nature of the salt prevented imbibed water from hydrolyzing the polymer so polymer erosion lagged behind drug release. If the matrix was mechanically weak, it ruptured and the basic salt was neutralized by the external buffer and homogeneous erosion occurred. In both cases it appeared that drug release was controlled by the swelling front and was independent of polymer erosion [172].

Naltrexone *in vitro* release from disks of soft and compliant Alzamer containing 10 wt% sodium carbonate and up to 30 wt% drug has been studied [173]. After a two-week induction period, naltrexone was released by zero-order kinetics and complete polymer erosion coincided with drug exhaustion. Similar devices made from glassy and tough Alzamer eroded more slowly than drug was released. Both systems increased in size and weight due to water absorption after implantation during *in vivo* studies. *In vivo* release from cylindrical Alzamer matrices containing sodium carbonate (10 wt%) and drug (20 wt%) was determined to be zero-order [160]. Theoretically, drug release from a heterogeneously eroding cylinder should decrease with time [128]. Schmitt hypothesized that the erosion rate of Alzamer increased at the appropriate rate to compensate for the decreased surface area of the cylinder. He suggested that an increase in hydronium ions and water at the matrix surface during erosion accelerated degradation since Alzamer hydrolysis is acid catalyzed [175]. No data were presented to verify this mechanism.

5. *Polyanhydrides*

The difficulty in achieving heterogeneous erosion using polyorthoesters is the stability of the backbone bonds and the need to include additives to promote erosion. To achieve such erosion, an equally hydrophobic polymer but with more labile backbone bonds may be required. Polyanhydrides which were originally suggested for use as clothes fibers but rejected because of their hydrolytic instability were chosen for this purpose. A prototype polyanhydride, poly(bis-*p*-carboxyphenoxy)methane, was synthesized and formed into disks and slabs by melt pressing. After a 20-d lag phase, linear heterogeneous erosion was observed for

up to 80% device erosion. When a relatively insoluble drug, cholic acid (10% loading), was incorporated in the matrix, release and erosion rates showed similar zero-order release [176, 177].

6. *Ideal Polymer System*

The requirements for an ideal bioerodible drug release matrix are that the polymer has or is 1) hydrophobic, 2) mechanical and physical integrity, 3) unswellable, 4) tight enough to prevent diffusion, 5) labile polymer backbone bonds, 6) polymer erosion intermediates and products which are nontoxic and readily eliminated or metabolized by the body, 7) no adverse tissue reaction, 8) a structure which is easily altered chemically to produce devices which have various lifetimes, 9) sidegroups or backbone bonds which are nonreactive with active agents, 10) easy to synthesize and work with, 11) stable on storage, and 12) reasonable in cost. Such a polymer could be formulated into a matrix device and display heterogeneous erosion. At present, no polymer meeting all these requirements has been developed.

B. Pendant Chain Systems

In this type of system a drug is chemically bound to a polymer backbone and is released by hydrolytic or enzymatic cleavage (Fig. 8). The use of these therapeutic agents has received considerable attention in drug-related research. The major thrust has been the design of polymer-drug complexes for short-term use that can reduce toxicity, increase therapeutic efficiency, or be targeted toward specific cells or organs [178–180]. At present, there have only been a few applications of pendant chain systems for long-term controlled release applications. Kim et al. have reviewed these pendant chain systems in detail [181].

In its simplest form, the pendant chain system appears as shown in Fig. 8, with drug attached to a soluble or insoluble polymer backbone. Soluble backbones are generally used for transport functions such as cell targeting; insoluble forms are more desirable for long-term controlled-release implants. The backbone may also be biodegradable or nonbiodegradable. For *in vivo* use, it is important that the polymers do not cause immunological reactions and that the drugs, when coupled to the polymers, do not function as haptens and induce allergic reactions. The drug itself can be attached directly to the polymer or it can be attached via a spacer group. The spacer group may be used to affect the rate of release and the hydrophilicity of the system [178].

To achieve near constant release, the cleavage of the drug from the polymer must be the rate-limiting step. Consider the cleavage of the pendant chain system given by the reaction

$$P\text{—}Dr + \text{cleaving agent} \xrightarrow{k} P + Dr$$

Then, if the rate of diffusion of the cleaving agent into the polymer matrix and the rate of diffusion of the drug, Dr, through the polymer matrix are much faster than the rate of cleavage, the release rate is limited by the chemical reaction above. Thus the release rate is constant only if the thermodynamic activity of the bound drug is constant with time, and the cleaving agent (e.g., acid, base, enzyme) is present in a certain volume.

One example of these systems is the polymers developed by Harris and coworkers [182] which contain herbicides such as 2,4-dichlorophenoxyacetic acid (2,4-D) or 2-(2,4,5-trichlorophenoxy) propionic acid (Silvex) as pendant side chains. This was done by first reacting these herbicides with the alcohol residues of desired acrylic esters. For example, Harris et al. reacted 2,4-D with an acrylic ester to form 2-acryloyloxyethyl-2,4-dichlorophenoxyacetate (2-A2,4-D). Polymerization of this derivative was then initiated by free radicals under mild conditions. Various modifications of this polymer-herbicide formulation were made by copolymerizing 2-A2,4-D with vinyl monomers containing hydrophilic residues such as trimethylamine methacrylamide (TAM). The mechanism of release was the hydrolysis of the herbicide—polymer ester bonds. This hydrolysis was not significant with the relatively hydrophobic homopolymers, but proceeded at a near constant value of 50 μg/d for 130 d when the hydrophilic TAM residues were included in the polymer backbone. These pendant chain systems offer an important advantage over other release systems in that over 80% by weight of the total delivery system is the drug itself. As economic considerations are a most important factor in agricultural applications, this compares favorably with many of the conventional systems that contain between 70-90% w/w of inert polymer carrier [182].

There has recently been interest in developing controlled-release systems using pendant chain polymers for clinical applications. Petersen and co-workers coupled norethindrone to the biodegradable polyaminoacid, poly(hydroxyalkyl)-L-glutamine and were able to release the drug at a near constant rate in rats for over 100 d [183].

V. SOLVENT ACTIVATED SYSTEMS

The rate of permeation of solvent can be used to affect the release rates for polymer matrices. There are two general mechanisms: osmosis (Fig. 13) and swelling (Fig. 14).

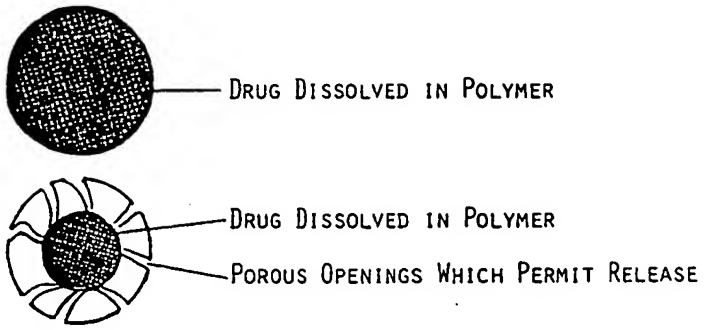

FIG. 13. Schematic diagram of a cross section of an osmotically-controlled matrix system.

A. Osmotically-Controlled Systems

The simplest osmotic device consists of a core containing bioactive agent which is surrounded by a semipermeable polymer film or membrane equipped with an orifice for delivery of the agent (see Fig. 15). If placed in contact with water or an appropriate biological fluid, water is transported through the membrane toward

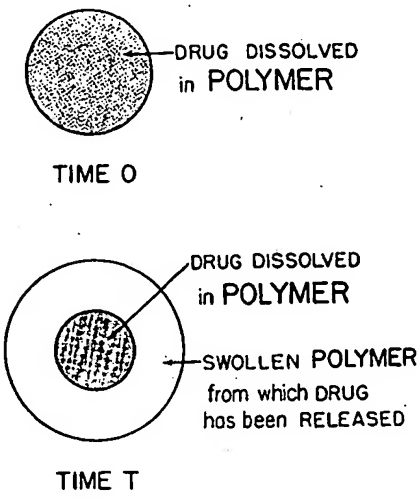

FIG. 14. Schematic diagram of a cross section of a swelling-controlled system.

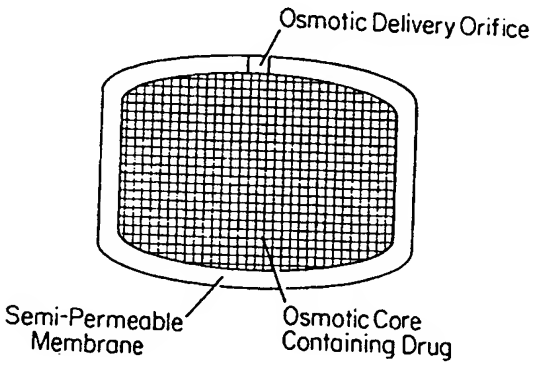

FIG. 15. Elementary osmotic pump (oros) cross section.

the core, resulting in release of equal volume of the solute solution through the orifice. This solution is usually at saturation, although more dilute solutions may be used.

Prediction of solute release in osmotically controlled systems is achieved by use of the Kedem-Katchalsky analysis of non-equilibrium thermodynamics [184]. According to this analysis the volumetric flux (total volume flow) J_V and the exchange flow J_D are defined according to Eqs. (46) and (47) for pseudobinary, thermodynamically ideal systems:

$$J_V = \overline{V}_i N_i + \overline{V}_w N_w = L_p \Delta P + L_{pD} \Delta \pi \tag{46}$$

$$J_D = \frac{N_i}{\bar{c}_i} - \frac{N_w}{c_w} = L_{Dp} \Delta P + L_D \Delta \pi \tag{47}$$

Therefore, the fluxes are expressed as linear relationships of the applied forces, namely the hydrostatic pressure difference ΔP and the osmotic pressure difference $\Delta \pi$. The terms $\overline{V}_i$ and $\overline{V}_w$ are the molar volume of solute and water, N_i and N_w are the solute and water fluxes with respect to stationary coordinates, and c_w and $\bar{c}_i$ are the water concentration and logarithmic average solute concentration, respectively. The terms L_p, L_{pD}, L_{Dp}, and L_D are the four Onsager coefficients. However, only three of these terms

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are necessary to describe solute diffusion through membranes, since according to Onsager's reciprocity theorem, $L_{pD} = L_{Dp}$.

The terms L_p and L_D represent the hydraulic and diffusive permeabilities of the membrane, respectively, and L_{pD} is a measure of the permselectivity of the membrane. Following Staverman's analysis [185], two new terms may be introduced according to Eqs. (48) and (49), the reflection coefficient σ and the permeability coefficient ω:

$$\sigma = -L_{pD}/L_p \tag{48}$$

$$\omega = (L_D - \sigma^2 L_p)\bar{c}_i RT \tag{49}$$

Any membrane may be fully described by L_p, σ, and ω. Then, the volumetric flow J_V may be rewritten in the more convenient form

$$J_V = L_p(\Delta P - \sigma \Delta \pi) \tag{50}$$

For an osmotically-controlled system which is initially loaded with solute above or at the solubility limit c_{is}, and solute concentration is kept constant and at a low level in the phase external to the device, $\Delta\pi$ is much larger than ΔP, and Eq. (50) can be written as

$$J_V = -L_p \sigma \Delta \pi \tag{51}$$

The volumetric flow is related to the change of osmotic pressure; the minus sign designates flow opposite to the osmotic pressure gradient. The osmotic pressure $\Delta\pi$ may be related to $\Delta c_{is} = c_{is} - 0$ as follows

$$\Delta \pi = -RT \Delta c_{is} \tag{52}$$

Moreover, the volumetric flow J_V may be expressed in terms of the equivalent solute release rate through the orifice of the device, dM_i/dt, as follows:

$$J_V = \frac{dM_i}{dt}\frac{\delta}{A} \tag{53}$$

where δ is the thickness and A is the area of the surrounding membrane. Then, from Eqs. (51), (52), and (53) one obtains

$$\frac{dM_i}{dA} = \frac{AL_p\sigma RT}{\delta}\Delta c_{is} = k_i\frac{A}{\delta}\Delta c_{is} \tag{54}$$

where

$$k_i = L_p\delta RT = \text{constant} \tag{55}$$

According to Eq. (54), osmotically-controlled devices of this form can release solutes at constant rates over a prolonged period of time, since Δc_{is} is constant and equal to the saturation concentration of the drug in water.

Upon complete dissolution of the solute in the device, the osmotic pressure cannot be assumed constant. Using Eqs. (51), (52), and (53), one can obtain for this case an expression of the solute release rate as in

$$\frac{dM_i}{dt} = k_1\frac{A}{\delta}(\Delta c_{is})^2 \tag{56}$$

These are the general equations obtained by Theeuwes using a similar derivation [185]. Further analysis using the specific geometry of the osmotically-controlled devices as well as simplified expressions of determination of the release rate, $dM_i/A\,dt$, can be found in the same contribution [185] and in the work of Wright et al. [186].

Three types of osmotically-controlled devices have received attention in recent years. A mini-osmotic pump (see Fig. 16) consists of a layered membrane in the form of a tube and a flow moderator which is inserted into the system after drug loading [187, 188]. The semipermeable membrane is made of a cellulose-based polymer and the osmotic driving agent is a potassium salt. A typical release curve of cumulative volume delivered by the system as a function of time is shown in Fig. 17. Zero-order release rates are obtained. These systems have been used for the release of viscous suspensions at constant rates. The amount delivered depends on the drug solubility [187].

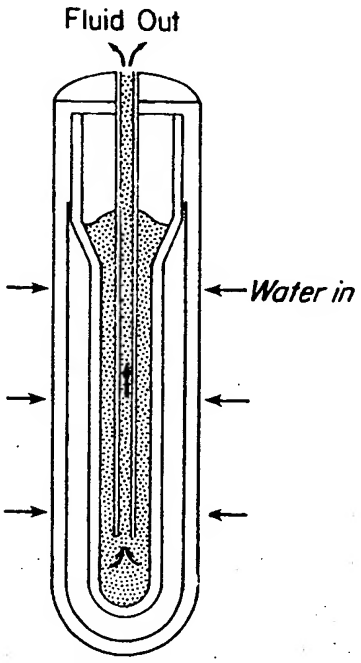

FIG. 16. Osmotic minipump [187].

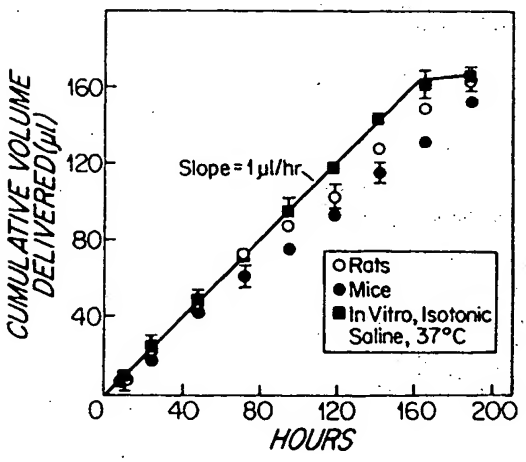

FIG. 17. Cumulative volume delivered from miniaturized osmotic pump.

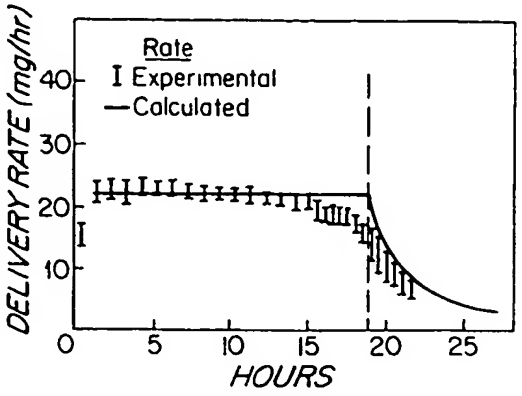

FIG. 18. In vitro release rate of potassium chloride from elementary osmotic pumps in water at 37°C. The experimental data were obtained from five systems. The calculated release rate is from Ref. 185.

The second system is an elementary osmotic pump manufactured under the trade name Oros (Fig. 15). Typical delivery curves of potassium chloride are shown in Fig. 18 [185]. Delivery rates are usually adjusted by varying the thickness of the semipermeable membrane. Matrix-type osmotically active systems where the drug is uniformly suspended in a polymer have also been reported [186] (Fig. 14). However, such systems have not generally released drugs at zero-order rates.

B. Swelling-Controlled Systems

Release of bioactive agents by swelling-controlled mechanisms is related to the diffusion of a solute from and through an originally glassy polymer under countercurrent diffusion of water or biological fluid into the polymer [62, 189]. Here we discuss only systems where solvent diffusion into the polymer leads to molecular conditions and relaxations which control solute diffusion.

In swelling-controlled polymeric systems the drug is originally dissolved or dispersed in polymer solution. Upon solvent evaporation, a solvent-free, glassy, polymeric matrix is obtained, with drug uniformly dispersed in it. This system constitutes a typical, swellable, pharmaceutical formulation [62]. Similar systems may be obtained by compression of particles of solvent-free polymer and drug, thus forming porous swellable systems [19, 20, 190].

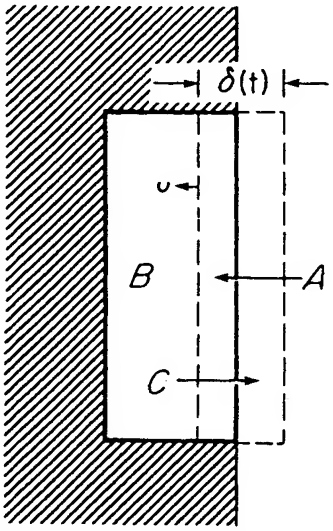

FIG. 19. Schematic representation of swelling-controlled release system. As the penetrant *A* enters the glassy polymer *B*, bioactive agent *C* is released through the gel phase of thickness $\delta(t)$.

Initially, there is no drug diffusion through the solid polymer phase. However, as the penetrant enters the matrix, the polymer swells, the glass transition temperature of the polymer is lowered below the temperature of the release experiment, and the swollen polymer allows the drug to diffuse outward.

Two fronts (interfaces) are characteristic of this swelling behavior: a front separating the glassy from the rubbery state (swelling interface), which moves toward the glassy state with velocity, v, and a front separating the rubbery polymer from the pure dissolution medium (polymer interface), which moves outward (see also Fig. 19). In the absence of molecular entanglements, the polymer will eventually dissolve. Dissolution of the polymer may be avoided if one works with semicrystalline, uncross-linked or with amorphous, slightly cross-linked polymers. In this case the crystallites and cross-links act as permanent junctions preventing dissolution. These systems are called swellable, nonerodible, release systems. Despite the existence of permanent junctions, dissolution of the polymer may occur due to chemical degradation (such as hydrolysis) or due to biodegradation.

Although many pharmaceutical formulations can be classified as swellable or solvent-activated systems, the term "swelling-controlled systems" is used to describe those formulations where the solute

release is actually controlled by the swelling phenomenon [5, 6, 62], namely by the relative position and velocity of the swelling interface.

In Section II-E-3 we presented characteristics of the effect of relaxations on solute diffusion through a swelling agent-activated polymer. Problems of mass transport accompanied by a change of phase are commonly known as Stefan problems or moving (or free) boundary problems [11]. An essential feature of these problems is the existence of moving surfaces separating the phases of the material. Some of the problems related to rigorous modeling of swellable polymers with solute release from them have been discussed recently [62–64, 190–192].

Drug release data from a glassy, polymeric slab under countercurrent, simultaneous diffusion of a swelling agent may be fitted to

$$M_t/M_\infty = kt^n \tag{57}$$

where M_t/M_∞ is the fraction of drug released at time t, and k and n are constants characteristic of the slab/dissolution medium system. Release rates can be fitted to the corresponding Eq. (58) which is readily obtained by differentiating Eq. (57):

$$\frac{dM_t}{A\,dt} = nc_d kt^{n-1} \tag{58}$$

where c_d is the initial loading of drug in the polymer in g/cm^3 of total sample.

Equations (57) and (58) describe the release kinetics of drugs which diffuse by Fickian mechanisms in nonmoving boundary problems. We have proven recently [64] that the swelling interface number, Sw, defined by Eq. (29) may be used as a sufficient and necessary criterion for the selection of drug/polymer/penetrant systems which exhibit zero-order release. This was proven with systems prepared by copolymerization of 2-hydroxyethyl methacrylate and methyl methacrylate in bulk. Figure 20 presents the general dependence of Sw on the exponent n of Eq. (58).

One of the earliest investigations with swelling-controlled release systems is attributed to Good [100] who studied the release of tripelennamine-hydrochloride from penetrant-free, glassy, cross-linked sheets analyzed in terms of Eq. (58). A significant portion of the release curve could be fitted to a straight line, indicative of zero-order release.

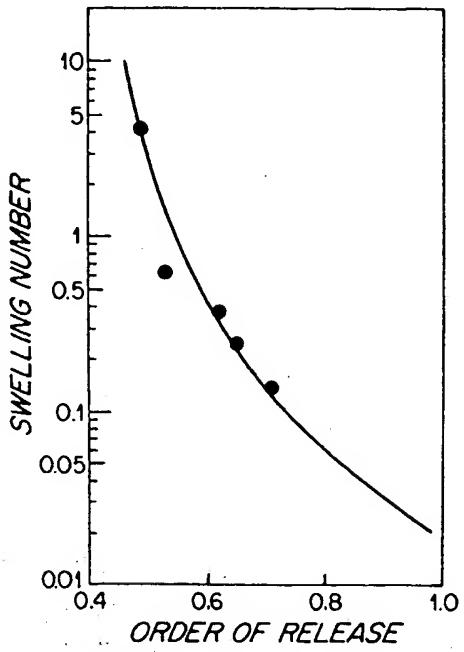

FIG. 20. Dependence of swelling interface number, Sw, on the magnitude of the exponent (order) of release (see also Eq. 56).

Demonstration of the potential of swelling-controlled systems to yield zero-order release kinetic behavior was offered by Hopfenberg and Hsu [62, 63, 189]. Sudan red dye IV was released from polystyrene in contact with *n*-hexane over a period of 60 h at constant rates. Use of the same technique for the release of various bioactive agents from ethylene–vinyl alcohol (EVA) copolymers into water did not produce zero-order release [193]. Non-Fickian solute release with $n \neq 0.5$ was observed.

EVA copolymers have attracted considerable attention as carriers for release of bioactive agents. They are prepared by hydrolysis of ethylene–vinyl acetate (EVAc) copolymers [114]. Depending on the conditions of hydrolysis and the initial molar ratio of the two monomers in the copolymer, copolymers of varying hydrophilicity can be prepared [113]. EVA sheets can be prepared by extrusion or molding. High or low temperature annealing has been used to introduce controlled degrees of crystallinity in the copolymer as a means of controlling the degree of hydrophilicity [194–196]. Other parameters affecting the equilibrium degree of swelling of these copolymers include the molecular weight [197], microstructure

[198], degree of cross-linking [199], and method of casting of the EVA films [197]. Dynamic and equilibrium swelling studies of different EVA copolymers in water and electrolytic solutions have been presented by Hopfenberg and his collaborators [193, 200].

Swelling-controlled release systems based on penetrant-free cross-linked poly(vinyl alcohol) (PVA) were recently discussed [9, 201]. Non-Fickian solute release with n as high as 0.76 was obtained. Possible modifications of the solubility of the polymer may lead to a swelling-controlled system with zero-order release. PVA systems can be prepared by preparation of aqueous PVA solutions which can be cross-linked by chemical or irradiative techniques [104–106] followed by evaporation of the water and annealing [107–109]. Copolymers of PVA with *N*-vinyl pyrrolidone (NVP) may be used upon drying [110].

Peppas and Franson [69] reported studies of solute release from P(HEMA-*co*-MMA) glassy polymers of HEMA mole fraction varying from 0.50 to 1.00. Dynamic swelling studies showed that these systems may be used for swelling-controlled release and that zero-order release could be achieved by increasing the hydrophilicity of the copolymer by progressively replacing MMA with a hydrophilic component, e.g., NVP.

Copolymers of MMA with HEMA and related hydroxylated acrylic monomers have been considered for controlled-release applications in diffusion-controlled devices at swelling equilibrium. They are prepared by reaction of the two monomers either in bulk or in ethanol/water mixtures [81, 202] in the presence or absence of cross-linking agents such as ethylene glycol dimethacrylate (EGDMA), triethylene glycol dimethacrylate (TGDMA), and related compounds [81]. Typical reaction temperatures range from 40 to 70°C and reaction temperatures range from 4 to 48 h. Copolymers produced by bulk copolymerization are solvent-free and may be used for swelling-controlled release systems. Their equilibrium degree of swelling depends on the comonomer feed ratio and the structure of the hydrophilic component (e.g., HEMA) [81, 202–204].

VI. MAGNETICALLY-CONTROLLED SYSTEMS

In these systems, drug and magnetic beads are uniformly dispersed within a polymer matrix. Upon exposure to aqueous medium, drug is released in a fashion typical of diffusion-controlled matrix systems. However, upon exposure to an oscillating external magnetic field, drug is released at a much higher rate.

Two types of magnetic systems have been designed. Both utilize ethylene–vinyl acetate copolymer. In one case, small mag-

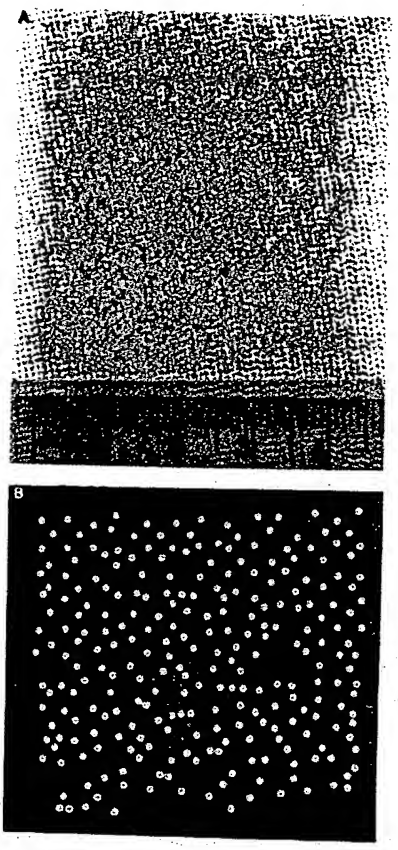

FIG. 21. A: Photograph of a magnetic polymer slab (magnification, 1.8×). B: X-ray photograph of magnetic polymer slab (magnification, 2.2×) [205].

netic beads (1.4 mm diameter) and drug are incorporated into a polymer slab (Fig. 21) [205, 206]. In the second case, a single Crucore magnet ring is inserted into a hemispheric device (Fig. 22) [207]. As discussed earlier, the hemisphere provides a near zero-order baseline release rate.

Several types of triggering devices have also been designed [208]. All of these require an oscillating magnetic field to induce triggering. In one case a permanent 1000 gauss bar magnet was placed on one end of a speed controlled rocker, which moved up and down vertically. The frequency was 18 cycles/min. In the second case, a motor was used in a device containing two Plexiglas

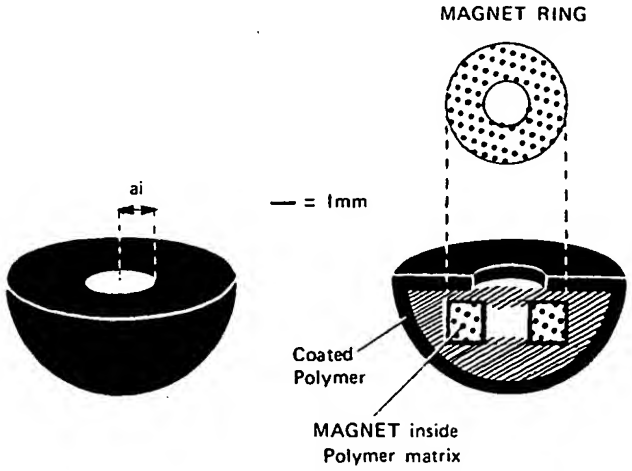

FIG. 22. Schematic diagram of a hemisphere magnetic pellet. All surfaces were coated with an impermeable barrier (black) except for a cavity on the flat surface [207].

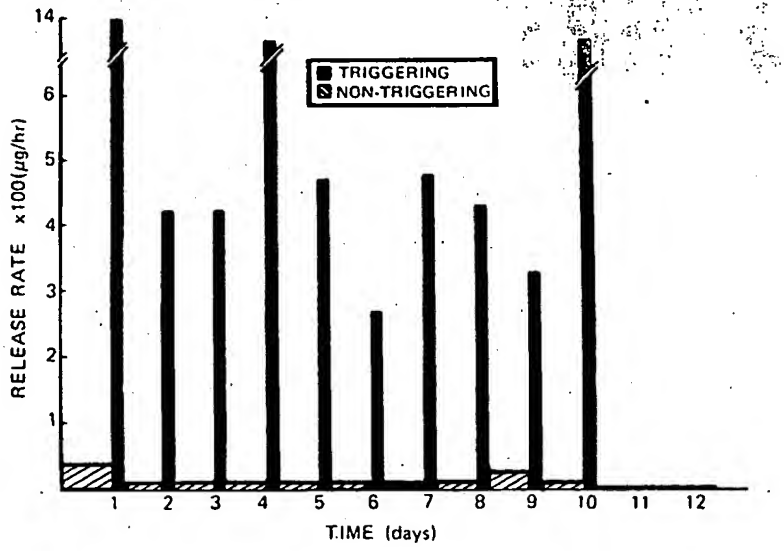

FIG. 23. Modulated controlled release of bovine serum albumin (BSA) from polymeric systems induced by magnetism. Each histogram represents the average release rate of BSA from eight polymeric systems. The systems were triggered for 5 h, followed by a resting period of 19 h [207].

disks to rotate the bottom disk which contained two bar magnets. The top disk containing vials with magnetic polymer slabs was held stationary. The frequency of rotation could be adjusted up to 400 cycles/min by means of a speed regulator.

Release rates up to 30-fold higher were observed when the oscillating magnetic field was turned on (Fig. 23). Initial tests also showed that these magnetic polymers displayed excellent tissue biocompatibility [206].

The mechanism responsible for magnetic modulation is unclear. It was mentioned previously that the incorporation of powdered drug into solvent cast ethylene–vinyl acetate copolymer caused pores to form within the polymer matrix [125]. It is possible that the beads cause alternating compression and expansion of the pores, thus facilitating release.

This delivery system allows external control of drug release rates and permits a modulated release pattern to occur. Such a system might have value in the treatment of diseases such as diabetes in which constant-rate insulin delivery supplemented by increased rates before meals has provided excellent control of blood glucose [209]. It might also be useful in birth control systems as a means of altering drug doses to correspond to the menstrual cycle.

VII. APPLICATIONS

Many applications of controlled-release systems such as in ophthalmic medications, contraception, and pesticides have been discussed in earlier sections of this paper. The purpose of this section is to discuss those applications in which controlled-release systems are most useful.

Medical applications of controlled-release systems can be divided into four general areas: oral systems, transdermal systems, external implants, and subcutaneous implants.

Oral medications are the most common and most popular type of dosage form. However, many drugs are not desirable candidates for oral-controlled release systems. In general, drugs that are poor candidates include those substances that have 1) long *in vivo* half lives, 2) wide differences between minimum effective dose and toxic level, 3) absorption limited to a narrow segment of the gastrointestinal tract, 4) high first-pass metabolism, and 5) requirements for large daily doses. Many drugs having these properties could probably be administered equally effectively using less sophisticated and less expensive techniques. Nonetheless, there are drugs which do have narrow therapeutic indices and where, if the drug exceeds the toxic level, undesirable side effects occur.

Such drugs include potassium, iron, and theophylline, all of which have been designed in controlled-release systems, generally in matrix forms. Several osmotic systems are currently being tested.

Transdermal systems are useful for a limited number of drugs which possess high skin permeability and are required in low doses. Skin permeability is dependent on the drug's ability to penetrate the stratum corneum. Drug permeability is described by Eq. (29); thus drug permeability through skin is a function of its molecular size, aqeuous solubility, and oil–water partition coefficient. Another limitation of transdermal systems is the time required before a steady-state plasma drug level is reached; this is usually 2 to 6 h. Thus, transdermal systems may be more useful for chronic rather than for acute situations. The major advantages of transdermal systems are that they reduce first-pass metabolism, and they are easy to apply and remove (compared to an implant). Several constant rate transdermal systems have been developed for nitroglycerin and scopolamine which last from 1 to 3 d. Reservoir systems have generally been used.

External implants are placed in locations such as the eye, uterus, vagina, or mouth (e.g., buccal membrane, teeth). Such systems can also avoid first-pass metabolism and can provide a simple method of delivering the drug locally thereby minimizing systemic effects. Examples include one-week systems for the release of pilocarpine to the eye [210], one-year systems for the release of progesterone to the uterus [211], six-month systems for the release of fluoride to the teeth [98], one-week systems for the release of tetracycline to the gums (for periodontal disease) [212], and one-day systems for the release of nitroglycerin through the buccal mucosa. All but the last of these systems are reservoir systems.

Subcutaneous implants are the least popular type of dosage form since an injection is required. However, for drugs which are not absorbed effectively orally, injections will generally be required. Macromolecules, in particular, are ideal candidates for subcutaneous implants since they are not absorbed orally and generally have short in vivo half lives. Examples of subcutaneous implants include dosage forms for narcotic antagonists [137], insulin [213], interferon [214], growth hormones, and vaccines [215]. These systems are generally matrices composed of erodible or nonerodible polymers. Such systems are still in experimental stages; none has yet been clinically approved.

Veterinary applications may be another major use for controlled-release systems. Candidates could include growth hormones, antiparasitic drugs, and drugs for estrous synchronization. Unlike human applications, controlled-release systems can be implanted in locations such as the ear (which can later be removed,

obviating the need for erodible polymers) or in the rumen of certain animals, thereby facilitating oral application.

Major applications of controlled release systems include those for pesticides, herbicides, molluscicides, and antifoulants. Numerous examples exist [216, 217]. Such systems generally prolong action and can decrease waste and cost. Matrix systems and pendant chain systems are most common because the cost of the system is an important consideration. Systems for household applications such as air fresheners, no-pest strips, and roach strips have also been developed. Cost is again a major consideration in these highly competitive markets.

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